

CRITICAL CARE UPDATE 2017



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Preface

Dear Friends

It is indeed a proud moment for Indian Society of Critical Care Medicine (ISCCM) to launch the first Critical Care Update 2017 book during its annual congress in Kochi. Over the years, attendance at ISCCM congress has been increasing exponentially and a scientific congress book highlighting the key topics discussed in the congress was long overdue. This book has around 80 chapters authored by national and international faculty covering all the major topics which will be discussed during the congress. This update will highlight the recent advances made in the field of critical care with special reference to its relevance and application in resource limited settings. A special section on "Economics of ICU" is worth mentioning. We sincerely hope this book will be useful both for young intensivists to promote analytical thinking, post graduates to keep abreast of recent advances, and also to senior clinicians. The publication of this book was possible only through a joint effort from the members of the editorial board, authors, and the publisher. We hope this book will continue to be published in the future congresses.

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Section 1



Hemodynamic Monitoring and Resuscitation

SECTION EDITOR: VIJAYA P PATIL

Fluid Therapy in Resource-limited Settings

Sameer A Jog, Maurizio Cecconi, Swapnil R Patharekar

INTRODUCTION

Intravenous fluid administration is the most common therapy used in the intensive care unit (ICU). Judicious use of intravenous fluids is essential in an ICU. The challenge is greater in limited resource settings since there is paucity of reliable parameters to guide fluid therapy. The “resource-limited setting” need not always be associated with economical as well as situational constraints like availability of appropriate ambulance or emergency room services in mass casualty situations.

Hypotension present at the hospital admission is associated with a significant mortality and studies have shown that early fluid therapy is associated with better outcomes.^{1,2}

On the other hand, overzealous fluid therapy is also associated with many complications, e.g., pulmonary edema. Excessive fluid administration may be proinflammatory and potentially injurious.^{3,4} It is, thus, imperative to know how to give the right amount of fluid.

Unfortunately, there is a paucity of good quality data in the field of fluid therapy. Hence, the decision-making in an individual patient is always a difficult task. Considering this background, optimum fluid therapy in a given patient, in a given setting, always remains a challenge for a treating physician even in a well-equipped, resource-rich ICU. In a resource-limited setting, this problem is even more complex.

DEFINING RESOURCE-LIMITED SETTING

When we say resource-limited setting in the context of intensive care medicine or emergency medicine, at least the following resources should be available for patient care. They are:

- Good clinical examination, especially to detect hypoperfusion
- At least 3-lead electrocardiogram monitoring for rhythm and rate
- Accurate noninvasive blood pressure measurement instrument

- Instrument for measuring oxygen saturation
- Facility for urinary catheterization and measuring half or one hourly urine output
- Peripheral intravenous access by a large bore cannulas
- In case of total vascular collapse—central venous access
- Necessary intravenous fluids like crystalloids and dextrose solutions
- Pressure bags to deliver the fluids at fast rate
- Oxygen therapy devices like oxygen cylinders, masks, and venturi
- Basic resuscitation drugs.

SHOCK^{5,6}

It is a life-threatening, generalized form of acute circulatory failure associated with inadequate perfusion to the tissues.¹ It could be hypovolemic, cardiogenic, obstructive, or distributive. The presentation of these shocks can overlap with each other, like patient presenting with shock due to hypovolemia owing to external blood loss can develop infection and lead to worsening of shock.

FLUID THERAPY

The most important physiological target of fluid administration is to improve tissue perfusion. Hemodynamic optimization with fluids has shown to improve patient outcome when applied in the early phases of sepsis and in the perioperative period.^{7,8} Fluid administration is, hence, considered as therapy.

The following points should be considered while administering fluid therapy in ICU in resource-limited settings.

Baseline Patient Demographics

This is one of the most important determinants of fluid therapy. Following patient groups barely respond to fluid and, in fact, overzealous fluid therapy in these patient groups can be detrimental.^{7,8}

- Chronic renal failure with anuria
- Acute coronary syndrome
- Acute and chronic decompensated heart failure
- Pulmonary embolism.

Indications

The indications relevant to resource-limited settings are:⁸

- Hypotension due to any cause
- Increased requirement of vasopressors
- Decreased urine output
- Increased skin mottling.

Most common indication for fluid therapy, as suggested by the Fluid Challenges in Intensive Care (FENICE)⁸ study, is hypotension due to any reason.

Type of Fluid⁷

Resuscitation fluids can be divided into two broad categories—colloids and crystalloids.

1. Colloids: The colloids are aqueous solutions that contain both large organic macromolecules and electrolytes. Colloids are subdivided into natural and synthetic colloids.
 - a. Natural colloid: Albumin is the prototype of natural colloid. It was also the first colloid solution used clinically. It is harvested from human plasma and is available in different concentrations like 4, 5, 20, and 25%.
Saline versus Albumin Fluid Evaluation (SAFE)⁹ and Albumin Italian Outcome Sepsis (ALBIOS)¹⁰ trials have clearly shown that use of albumin does not offer any advantage over crystalloids. In fact, use of albumin can be detrimental in patients with traumatic brain injury.¹¹ Though there is some advantage for using albumin in early sepsis,¹² the evidence is not strong enough to recommend its use in resource-limited settings. The cost of albumin is also a deterring factor to use it in these settings.
 - b. Synthetic colloids:⁷ They are divided into three groups—starches [hydroxy ethyl starch (HES)], gelatins, and dextran. These colloids were promoted as cheaper alternative to albumin.
 - i. Gelatins: These are derived from bovine gelatin, their colloid base is protein.
 - ii. Dextran: It is a carbohydrate based colloid. Bacteria make this polysaccharide molecule during ethanol fermentation.
 - iii. Hydroxy ethyl starch: Hydroxy ethyl starch are derived from the starch of potatoes or maize, and their colloid base is a large carbohydrate molecule. Solutions of molecular weight like 130, 200, and 450 kD are available.

Based on current evidence, colloid use is not recommended in the ICU. Colloid usage has shown to increase incidence of acute kidney injury (AKI)

and need for renal replacement therapy.^{13,14} Though there is some controversy due to emerging evidence from recent trials,^{15,16} the overall consensus is to avoid their usage in the ICU. Also, as colloids are costlier than crystalloids, their usage in resource-limited settings is limited.

2. Crystalloid solutions: These fluids are the first choice for fluid resuscitation. They are well-tolerated and inexpensive.
 - a. Sodium chloride (saline): This is the most commonly used crystalloid solution globally. There are few concerns about the high chloride content of normal saline, incidence of hyperchloremic metabolic acidosis, and renal replacement therapy;^{17,18} then again, evidence is not strong enough to discard its use routinely.
 - b. Balanced or physiological solutions: These are derivatives of Hartmann's and Ringer's solutions. Due to their cost, regular use of these fluids in resource-limited settings is not recommended. In addition, currently there is no strong evidence to support the routine use of balanced crystalloids in the ICU.¹⁹

Volume and Dose

It is very difficult to generalize dose and volume of fluid. The requirements as well as response vary greatly during the course of any critical illness. Also, no single physiological or biochemical parameter is particularly useful to decide about fluid responsiveness. However, systolic hypotension and oliguria are used as triggers to administer a fluid challenge. It ranges from 200 to 1,000 mL of crystalloid for an adult patient.

Surviving Sepsis Campaign has recommended an initial fluid resuscitation of 30 mL/kg of crystalloids in septic patients with hypotension and/or lactate more than 4 mmol/L. A fluid challenge should consist of a volume large enough (no more, no less in theory) to raise the mean systemic filling pressure²⁰ and increase venous return (cardiac output) in a preload responsive patient. Also, importantly, fluid resuscitation needs to be individualized to the patients need and clinical indication. In the perioperative period volumes between 250 and 500 mL of fluids is routinely used.²¹ Most studies involving nonsurgical patients have used fluid challenges of 500 mL given within 30 minutes.²²

Initiation and Endpoints

In resource-limited settings, where advanced laboratory testing or hemodynamic monitoring are lacking, the task of identifying early stages of circulatory dysfunction mainly relies on proper clinical examination and basic laboratory testing.

Heart Rate

Heart rate (HR) is an easily available tool to assess fluid responsiveness in resource-limited settings. The contribution of HR to cardiac output and regulation of blood pressure

is crucial. Tachycardia is an important early sign of shock.⁵ However, tachycardia in shock could partly be due to other factors, including pain, stress, or anemia. In addition, bradycardia could be present in severe hypovolemia. The specific value of HR to guide resuscitation has been poorly studied. It is also obvious that a decrease in HR after a fluid challenge indicate fluid responsiveness. However, the HR responses in studies testing the fluid responsiveness in ICU patients were variable. While some studies found a significant decrease in HR after fluid administration in responders,²³ others reported no change in HR after fluid challenge in spite of having a significant increase in cardiac index.²⁴ Therefore, HR alone cannot be used to predict fluid responsiveness.

Blood Pressure

Components of blood pressure are²⁵ systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and pulse pressure (PP).

Systolic arterial pressure

A SAP value lower than normal (e.g., 90 mmHg) may be associated either with a normal DAP (e.g., 80 mmHg) or a low DAP (e.g., 50 mmHg). If PP is not low, then no clear information on stroke volume can be drawn. Also, if pulse pressure is low as in first case, stroke volume is expected to be low, especially in cases of stiff arteries. Knowledge of the sole value of SAP is, thus, not good guide to decide about requirement of intravenous fluids.

Diastolic arterial pressure

The factors which determine DAP are arterial tone and HR. Therefore, a low DAP (e.g., 50 mmHg) suggests a low arterial tone, especially in the case of tachycardia. A low DAP, thus, is indication for use of vasopressor, although fluids can also be given in septic shock patients. Hence, DAP value alone also cannot indicate fluid requirement.

Mean arterial pressure

A low MAP may be associated with cardiogenic shock (right or left) for which fluid therapy can be detrimental. Conversely, during hypovolemia, MAP can be maintained due to compensatory mechanisms that increase vascular resistance. Thus, any particular level of MAP as trigger for fluid challenge can be misleading.

Again, MAP alone may not be sufficient to determine adequacy of fluid resuscitation. An increase in MAP after fluid challenge may indicate positive response but absence of it does not suggest that patient is not fluid responsive.

Pulse pressure

A low PP suggest low stroke volume and in the presence of shock, this would encourage fluid administration, unless signs of pulmonary edema are present. However, the need of fluid therapy is not absolutely certain since low stroke

volume can also be due to cardiac failure. In patients with stiff arteries due to aging or comorbidities, PP may not be low in spite of low stroke volume.

In spite of this, changes in PP follow the changes in cardiac output induced by fluid infusion more reliably than MAP.

More importantly, results are more or less similar irrespective of the method of measurement of arterial blood pressure which may be arterial catheter or noninvasive oscillometric automated brachial cuff. Also, the presence of arrhythmias do not change the results.²⁶ Hence, PP is one of better index for fluid administration in resource-limited settings.

Shock Index

Shock index (SI) is the ratio of HR divided by SAP (HR/SAP). Normal value for SI range is 0.5–0.7 in healthy adults. Since isolated HR or SAP may not be sufficient to detect early phases of shock or hypovolemia. An SI was originally described in trauma patients.⁹ Shock index has a linear inverse relationship to cardiac output and stroke volume.¹⁰ An SI ≥ 1.0 has been associated with a bad outcome in shock patients.²⁷ In trauma patients, it can be used to stratify patients for increased transfusion requirements and early mortality.²⁸ Therefore, it is considered as the most important vital sign to detect acute hypovolemia and circulatory failure in trauma patients. It has also shown relevance in septic shock patient as well and correlate well with lactate levels. In summary, SI is one of easiest, reliable, and inexpensive vital sign which can be used in patients with shock to determine volume responsiveness.

Capillary Refill Time

It is defined as the time taken for color to return to an external capillary bed after pressure is applied to cause blanching. It can be measured by holding a hand higher than heart level and pressing the soft pad of a finger or fingernail until it turns white, then taking note of the time needed for the color to return once pressure is released.²⁹

Normal values for capillary refill time (CRT) are <2 seconds in young individuals and values up to 4.5 seconds are normal in the elderly.²⁹ Capillary refill time can assist in assessment and prognostication of trauma, major abdominal surgery, and early septic shock patient.^{29–32} Patients with abnormal peripheral perfusion presented with higher lactate levels and have a higher incidence of circulatory complications.

Capillary refill time is a rapid flow-responsive parameter that can be used in limited-resource settings as a trigger and response during fluid resuscitation.³³ A recent study has demonstrated that the use of CRT as a guide for fluid therapy is associated with almost 2 L of lesser fluids in comparison to the classic approach, and also to a lesser organ dysfunction.³²

Despite this, it was used as a trigger for fluid resuscitation in less than 8% of cases in the FENICE trial.⁸ Limitations for use of

CRT can be interobserver variability, skin color, and influence of ambient temperature.²⁹ In spite of this, ease of doing it and valuable information that it can give, this parameter needs justice in resource-limited settings. Routine use of CRT is highly recommended for trigger, guide, prognostication, and stratification during fluid resuscitation process. Normal CRT after fluid challenge denotes good prognosis while the opposite is associated with increased mortality.

Mottling Index

Mottling is defined as patchy skin discoloration that usually starts around the knees. It is due to heterogeneous, small vessel vasoconstriction, and is thought to reflect abnormal skin microperfusion. Mottling is easily available sign that can be used for assessment of circulatory dysfunction.³⁴

It has been shown to predict mortality in septic shock. Mottling is quantified according to a mottling score. Score varies between 0 and 5. A higher score correlates with increased mortality. High doses of vasopressors can also increase skin mottling and lead to purpuric changes.

Jugular Venous Pressure

The jugular venous pressure (JVP) is the indirectly observed pressure over the venous system via visualization of the internal jugular vein.³⁵ The patient is positioned at 30°, and the filling level of the internal jugular vein determined. In healthy people, the filling level of the jugular vein should be <3 cm vertical height above the sternal angle. Low JVP usually indicated fluid responsiveness. With high JVP, one should be cautious about fluid resuscitation.³⁵ There are many limitations of JVP, like assessment of JVP is technically complex, difficult to interpret, and is very subjective. The JVP also does not correlate well with CVP. More importantly, it can be used as a safety limit for fluid resuscitation. A significant increase in JVP before or during fluid resuscitation should alert clinician of fluid overload.

Urine Output

During early shock, multiple neurological and hormonal mechanisms get activated to maintain blood flow to vital organs including kidney. Secondary functional changes in renal blood flow, glomerular filtration, or tubular function may result in oliguria.³⁶ However, oliguria is a nonspecific symptom and could also be present in mild dehydration without hypoperfusion and in major surgery which may or may not reflect renal or systemic hypoperfusion during early shock. Importantly, during septic shock and post major surgery, the presence of profound intrarenal microcirculatory abnormalities that are triggered by proinflammatory mediators are the main mechanisms for pathophysiology

of AKI than hypoperfusion and these abnormalities do not revert with systemic flow increasing maneuvers.³⁶

Despite these limitations, oliguria is used as a trigger and target for fluid resuscitation in 18% patients.⁸ On the contrary, several studies have shown that positive fluid balance is associated with morbidity and mortality in patients with AKI in different settings.³⁷ Fluid overload in these situations may lead to cardiac dysfunction and intra-abdominal hypertension which may hasten the onset of AKI and perpetuate oliguria.

Blood Lactate Levels³⁹ (Box 1)

The normal serum lactate level in resting humans is approximately 1 mmol/L (0.7–2.0). The value is the same in venous or arterial blood. Use of a tourniquet can lead to pseudoelevation of lactate level. An increase in serum lactate levels may indicate poor tissue perfusion. Large data are now available to indicate serum lactate levels as an appropriate target for fluid resuscitation, and is recommended to use as surrogate measure of tissue microperfusion. Repeated measurements of lactate concentrations over time are particularly useful for monitoring the response to therapy.

Box 1: Factors that may contribute to hyperlactatemia

- Increased production of lactate
 - Tissue hypoxia
 - Increased aerobic glycolysis
 - Inhibition of pyruvate dehydrogenase (in sepsis)
 - Methanol/ethylene glycol/propofol toxicity
 - Thiamine deficiency
- Decreased clearance of lactate
 - Liver dysfunction or failure
 - Cardiopulmonary bypass (minor reduction in clearance)
- Exogenous sources of lactate
 - Lactate buffered solutions used in continuous venovenous hemodiafiltration
 - Medications (metformin, nucleoside reverse transcriptase inhibitors, long-term linezolid use, intravenous lorazepam, and valproic acid)
 - Hematologic malignancies

CONCLUSION

Appropriate fluid therapy in a resource-limited setting is really a challenging issue. On the background of paucity of evidence based guidelines, this task is more complex. Use of basic parameters and sound understanding of physiology will definitely enhance the decision-making ability of a physician. However, at the bedside in an emergency situation, one may have to use his/her own discretion to answer the million dollar question “how much fluid?”

REFERENCES

- Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med.* 2014;40:1795-815.
- Hamilton MA, Cecconi M, Rhodes A. A systematic review and metaanalysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg.* 2011;112:1392-402.
- Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. *Chest.* 2008;133:252-63.
- Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-75.
- Vincent JL, De Backer D. Circulatory shock. *N Engl J Med.* 2013;369:1726-34.
- Babaev A, Frederick PD, Pasta DJ, et al; NRM Investigators. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA.* 2005;294:448-54.
- Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369:2462-3.
- Cecconi M, Hofer C, Teboul JL, et al; FENICE Investigators; ESICM Trial Group. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med.* 2015;41(9):1529-37.
- Finfer S, Bellomo R, Boyce N, et al; The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350:2247-56.
- Caironi P, Tognoni G, Masson S, et al; The ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370:1412-21.
- Cooper DJ, Myburgh J, Finfer S, et al. Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? *J Neurotrauma.* 2013;30(7):512-8.
- Finfer S, McEvoy G, Bellomo R, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med.* 2011;37:86-96.
- Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med.* 2012;367:124-34.
- Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med.* 2012;367:1901-11.
- Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care.* 2012;16:R94.
- Anname D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA.* 2013;310(17):1809-17.
- Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA.* 2012;308(15):1566-72.
- Yunos NM, Bellomo R, Glassford N, et al. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med.* 2015;41:257-64.
- Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA.* 2015;314(16):1701-10.
- Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? *Curr Opin Crit Care.* 2011;17:290-5.
- Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: Goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. *Crit Care.* 2013;17:209.
- Eskenes TG, Wetterslev M, Perner A. Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. *Intensive Care Med.* 2016;42:324-32.
- Jabot J, Teboul JL, Richard C, et al. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med.* 2009;85-90.
- Pottecher J, Derudder S, Teboul JL, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. *Intensive Care Med.* 2010;36(11):1867-74.
- Le Manach Y, Hofer CK, Lehot JJ, et al. Can changes in arterial pressure be used to detect changes in cardiac output during volume expansion in the perioperative period? *Anesthesiology.* 2012;117:1165-74.
- Lakhal K, Ehrmann S, Perrotin D, et al. Fluid challenge: tracking changes in cardiac output with blood pressure monitoring (invasive or non-invasive). *Intensive Care Med.* 2013;39:1953-62.
- Rady MY, Rivers EP, Martin GB, et al. Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock. *Am J Emerg Med.* 1992;10:538-41.
- Mutschler M, Nienaber U, Münzberg M, et al; TraumaRegister DGU. The shock index revisited—a fast guide to transfusion requirement? A retrospective analysis on 21,853 patients derived from the TraumaRegister DGU. *Crit Care.* 2013;17:R172.
- Limq A, Bakker J. Clinical assessment of peripheral circulation. *Curr Opin Crit Care.* 2015;21:226-31.
- van Genderen ME, Engels N, van der Valk RJ, et al. Early peripheral perfusion-guided fluid therapy in patients with septic shock. *Am J Respir Crit Care Med.* 2015;191:477-80.
- van Genderen ME, Paaue W, de Jonge J, et al. Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. *Crit Care.* 2014;18:R114.
- Ait-Oufella H, Bige N, Boelle PY, et al. Capillary refill time exploration during septic shock. *Intensive Care Med.* 2014;40:958-96.
- Hernandez G, Pedreros C, Veas E, et al. Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation. A clinical-physiologic study. *J Crit Care.* 2012;27:283-8.
- Coudroy R, Jamet A, Frat JP, et al. Incidence and impact of skin mottling over the knee and its duration on outcome in critically ill patients. *Intensive Care Med.* 2015;41:452-9.
- Chua Chiao JM, Parikh N, Fergusson D. The jugular venous pressure revisited. *Clev Clin J Med.* 2013;80:638-44.
- Prowle J, Bagshaw SM, Bellomo R. Renal blood flow, fractional excretion of sodium and acute kidney injury: time for a new paradigm? *Curr Opin Crit Care.* 2012;18:585-92.
- Payen D, de Pont AC, Sakr Y, et al; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care.* 2008;12:R74.
- Eskenes TG, Wetterslev M, Perner A. Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. *Intensive Care Med.* 2016;42:324-32.
- Wacharasint P, Nakada TA, Boyd JH, et al. Normal-range blood lactate concentration in septic shock is prognostic and predictive. *Shock.* 2012;38(1):4-10.

How Much Fluid is Too Much Fluid?

Srinivas Samavedam

INTRODUCTION

Intravenous fluid therapy is one of the most common interventions performed on hospitalized patients. Patients in the emergency room, intensive care unit (ICU), and operating room probably receive this intervention more often than others. Fluid therapy, when driven by scientific rationale and principles is the cornerstone of most resuscitation algorithms. The benefits of prompt fluid resuscitation in terms of organ perfusion, hemodynamics, and acid-base homeostasis cannot be overemphasized. However, like any other pharmacological intervention, fluid therapy, when excessive can increase the mortality and adds to the morbidity of critically ill patients. It is, therefore, important to know the limits to which this intervention can be stretched. This review will attempt to summarize the methods of identification of fluid overload (FO) and the parameters which define too much fluid.

IS THIS A RELEVANT QUESTION?

The adverse effects of fluid therapy, which is either delayed or denied, are well known. The effects of sedatives and vasoactive drugs are also influenced by the volume status of an individual. However, over the last decade or so, evidence has emerged, questioning the unmeasured and unqualified administration of fluids. In fact, fluid therapy during critical illness has been labeled a double-edged sword.¹ The advent of bioimpedance, widespread availability of ultrasonography (USG), reemergence of thermodilution techniques for the assessment of extravascular lung water (EVLW), coupled with the understanding of the nature of the endothelial glycocalyx, have shed more light on the adverse effects of positive fluid balance (PFB) on the outcomes of critically ill patients.

WHAT DOES POSITIVE FLUID BALANCE DO?

Almost every organ system suffers from the adverse effects of PFB. The most well-recognized complication of PFB is

TABLE 1 Side effects of a positive fluid balance

Site	Adverse effects
Brain	Cognitive changes delirium
Myocardium	Contractility change, diastolic dysfunction, conduction disorders
Lungs	Gas exchange effects, compliance change
Liver	Cholestasis, synthetic dysfunction
Kidneys	Glomerular filtration rate reduction, salt and fluid retention
Bowel	Malabsorption, ileus, compartment syndrome
Peripheral tissues	Microcirculatory changes, delayed wound healing

intra-abdominal hypertension. Encapsulated organs, such as the liver and kidney, have limited capacity to accommodate excessive interstitial fluid. As a result, PFB results in a reduced perfusion or venous drainage of such organs resulting in ischemic injury. Table 1 depicts the adverse effects of PFB on various organ systems. Enough evidence exists in literature outlining the consequences of PFB on several outcomes among critically ill patients. This has included patients enrolled in medical,^{2,3} surgical,⁴ and burns⁵ ICUs. The adverse effects include worsening of pulmonary function, delayed renal recovery, compromise in myocardial contractility, and rise in intracranial pressures. Minor outcomes like wound healing, pressure sores, and cholestasis were also adversely influenced by delayed PFB.⁶

WHAT DO WE USUALLY TARGET DURING FLUID RESUSCITATION?

Traditionally, fluid challenge and resuscitation have been triggered by clinical and pathophysiological parameters or by identification of markers of tissue hypoperfusion. Oliguria has always been a trigger for fluid challenge, on the valid assumption, that oliguria is a marker of decreased cardiac

output. A fluid bolus is presumed to increase the cardiac preload translating into enhanced cardiac output.⁷ However, persistent oliguria should be viewed as a marker of organ dysfunction rather than as a marker of reduced preload. Continued attempts at fluid challenges after the initial phase could predispose to significant PFB.

Lactate is another marker, which triggers a decision of fluid therapy. Although lactate clearance is a reliable indication of a successful resuscitation, persistent elevation of lactate has multiple confounding causes including hepatic clearance and systemic oxygenation. Continuing to resuscitate a patient based solely on lactate values might not achieve the desired results.

Static parameters, like central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP), have been proven to be unreliable markers of either hypovolemia or FO. They seem to be incapable of predicting the effect of a fluid bolus on the cardiac output. It is now an accepted fact that more than half the patients with a low CVP are actually unresponsive to fluids. Targeting a normal CVP for these patients is more likely to result in an ineffective PFB.

Variations in stroke volume induced by mechanical ventilation have been an established indicator of preload status of both ventricles. However, it is equally well-known that its applicability to a spontaneously breathing patient as well as to a patient with a nonsinus rhythm is not valid. Moreover, the validation of this variation relates to tidal volumes, which are much higher than what is currently prescribed as safe. Considering the fact that fluid balance plays a crucial role among patients with acute respiratory distress syndrome (ARDS), where tidal volumes are maintained low, the application of stroke volume variation to limit fluid therapy appears impractical.⁸

DO WE HAVE BETTER TOOLS?

Current availability of ultrasound, bioimpedance, and less invasive methods of thermodilution makes EVLW and pulmonary vascular permeability index measurements feasible. Similarly, widespread availability and increasing understanding of the dynamics of brain natriuretic peptide (BNP) have made this biomarker a potential candidate for assessing FO. Intra-abdominal pressure monitoring might be another potential candidate.⁹

Extravascular Lung Water

Extravascular lung water is the amount of water that is contained in the lungs outside the pulmonary vasculature.¹⁰ It is influenced by multiple fluid inputs—alveolar, interstitial, intracellular, and lymphatic. However, pleural effusions do not form part of EVLW. The volume of EVLW is mainly controlled by the lymphatic system, which returns the volume to the systemic circulation. The normal value of EVLW indexed to body weight is <7 mL/kg body weight.

How is Extravascular Lung Water Measured?

The gross method to assess EVLW is by a chest X-ray (CXR). However, there is always a scope for interobserver variability in interpretation. Moreover, the exact index of EVLW when pulmonary edema appears on CXR was never studied. From a theoretical standpoint, the gold standard method of assessment of EVLW would be gravimetry, which implies weighing the lung *ex vivo* before and after drying out. This automatically excludes its applicability in clinical practice. Several other methods have been described for measuring EVLW, each with its own strong and weak points. Table 2 depicts the characteristics of these tests.

Currently, transpulmonary thermodilution and lung USG seem to be practical methods of assessment of EVLW. The role of USG in measuring EVLW will be discussed later in this review.

Transpulmonary thermodilution has emerged as a tool, which is validated experimentally against gravimetry. The principle revolves around a central venous catheter inserted in the superior vena cava territory coupled with a femoral thermistor-tipped arterial catheter. Cold saline is injected into the venous catheter and the decrease in temperature is measured at the arterial catheter. This will yield a thermodilution curve. Using this curve, the EVLW is estimated by using the Stewart-Hamilton principle. As per this principle, the intrathoracic thermal volume (ITTV) is assessed as a product of cardiac output and mean transit time. The difference between the total pulmonary volume and the ITTV will represent global end-diastolic volume (GEDV). Multiplying the GEDV with a factor of 1.25 gives the intrathoracic blood volume (ITBV). The difference between ITTV and ITBV yields the EVLW. Extravascular lung water has been shown to have a good correlation to mortality among critically ill patients, especially, those with sepsis and ARDS.¹⁰⁻¹³ This is the subset of patients, who are likely to be adversely affected by a PFB. Although traditionally EVLW has been indexed to body weight, scientifically, indexing it to the height of the individual appears to be a more robust system.

Brain Natriuretic Peptide

Serum BNP is a neurohormone, whose release is a direct consequence of increase in ventricular wall tension. One of the advantages of BNP as a marker of wall stress is its short half-life (<20 minutes). In effect, this implies that an elevated BNP almost always indicates a recent increase in ventricular wall stress. Sepsis and ARDS are both conditions where early detection of PFB is likely to improve the ultimate outcome. A sustained rise in BNP might indicate an increased fluid related ongoing stress on the ventricular wall. Zhang et al.¹⁴ evaluated the prognostic value of BNP and its potential role in guiding fluid therapy among septic patients. While admission BNP was an independent predictor of mortality, Δ BNP correlated with other outcomes such as

TABLE 2 Methods of assessment of extravascular lung water

Method	Accuracy	Clinical value	Cost
Gravimetry	Reference experimental technique	Nil	Low
Chest X-ray	35% increase in EVLW is needed to show pulmonary edema	Can miss interstitial edema	Low
Computed tomography	Regional changes picked up	Cannot be used bedside, nonspecific	High
Magnetic resonance imaging	EVLW cannot be subtracted from intravascular volume	Long-image acquisition time. Not bedside	High
Positron emission tomography	EVLW can be separated from total water by ^{15}O labeled carbon monoxide	Not meant for repeated assessments	Very high
Bioimpedance	Does not differentiate intrathoracic fluid	Alternative to dye dilution	Low
Multiple inert-gas-exchange technique	Assesses only EVLW accessible to airways	Not uses	Relatively low
Double thermo-dye dilution	Uses heavy water that increases accuracy	Invasive, cumbersome	Relatively high
Single thermos dilution	Acceptable	Repeated measurements possible	Relatively low

EVLW, extravascular lung water.

ICU length of stay and duration of ventilation. In addition, the authors reported that the BNP values could change with as little as 100 mL of PFB. A Brazilian study involving close to 100 patients in the outpatient demonstrated a good correlation between the presence of B lines on lung USG and elevation of BNP levels.¹⁵

While the significance of B lines and their correlation with EVLW will be discussed in the following paragraphs, the relevance of BNP to the sonographic pattern of FO needs to be noted.

Lung Ultrasonography

Assessment of the lungs by sonography has become standard of care in most ICUs. The readily availability, noninvasive nature, replicability, and lack of radiation hazard make USG an ideal tool for repeated assessment of lung abnormalities. Definite profiles have been identified to represent interstitial fluid, alveolar fluid, and extraparenchymal collections. Lung USG has the ability to identify interstitial edema, which precedes pulmonary edema.¹⁶ A definite change in profile represents the appearance of interstitial edema, which warrants cessation of fluid therapy.

HOW MUCH IS TOO MUCH?

Clinical Evaluation

Clinical examination is a useful tool for identifying signs of FO in an outpatient setting. Sacral edema and pedal edema would be useful markers of a PFB in an ambulant patient. However, in a critically ill, bed-bound, hypoalbuminemic patient receiving vasopressor support will always have some degree of these clinical markers. Early detection of FO in this subset of patients is, therefore, likely to need other

markers. Conjunctival edema, pleural effusions, etc. are not consistent and are more likely to be delayed markers of FO. Measurement of IAP could be a useful tool for identification of PFB. Grades of intra-abdominal hypertension are well-validated. In a patient, who has undergone fluid resuscitation, it may be pertinent to initiate the measurement of IAP at least for the first 72 hours, when the risk of PFB is high. Progress of IAP beyond grade I should be viewed with caution and should trigger a more meticulous attention to fluid balance in the least. This will particularly be valid among patients with generalized increase permeability states.

Chart Review

A meticulous review of the fluid balance for daily as well as cumulative PFB could be the simplest method to identify and correct a PFB of clinical significance. Literature review shows enough evidence linking a PFB with worse outcomes amongst a wide subset of critically ill patients.

The Fluids and Catheters Treatment Trial (FACTT) is probably the most well-recognized publication, which draws attention to the deleterious effects of PFB of as little as 1.1 L in 24 hours, while also questioning the relevance of CVP and PAOP.¹⁷ Lee et al. studied the association between fluid balance and survival among critically ill patients.¹⁸ The authors identified a hazard ratio of 1.04 for dying with a positive balance of 1 L on day 2, within 90 days of ICU discharge. This hazard ratio was 1.07 for ICU mortality. This effect was even more pronounced amongst those who had a condition predisposing to fluid retention like acute kidney injury and congestive heart failure. Cumulative fluid balance seems to have a greater impact on mortality than the peak PFB. The Randomized Evaluation of Normal vs. Augmented Level (RENAL) study demonstrated the beneficial effects of a net negative balance on 90-day survival

among critically ill patients.¹⁹ The authors recommended a goal of negative fluid balance after the initial phase of resuscitation. Pradeep et al. evaluated the role of fluid volume administered on the outcome of patients undergoing cardiac surgery.²⁰ They identified that a PFB of >500 mL in the immediate postoperative period, identified those, who went on to develop a cumulative PFB. They also identified an intraoperative fluid volume of 4 L as a clue for identifying those who will develop a PFB. Bouchard et al.²¹ showed that a weight increase of >10% over the baseline defines those who develop a cumulative PFB.

In summary, a meticulous chart review is mandatory to avoid PFB. Attention should focus on avoiding a PFB >1 L.

Extravascular Lung Water

As discussed earlier, EVLW has a strong physiological rationale for application to the problem of FO and PFB. Chung et al. studied the impact of EVLW index on the outcome of patients with severe sepsis.²² Although the sample size was very small, the authors were able to identify a value of 10 mL/kg as a cutoff for safe EVLW index. They were also able to show a fourfold increase in mortality among septic patients who had an EVLW index >10 mL/kg. Pino-Sanchez et al. studied the influence of EVLW index on decision making pertaining to fluids and vasoactive therapy.²³ In this study, an EVLW index >9 mL/kg triggered a decision to reduce fluid volume and a value >14 mL/kg triggered an aggressive diuretic strategy among hypoxic patients. For patients in hypotension, undergoing resuscitation, a value of 9–14 mL/kg was a trigger for stopping fluid therapy. Another relevant point from this study was that patients with EVLW index >9 mL/kg were considered to be clinically euvolemic. The CVP also did not differ significantly between those, who had values greater or lesser than 9 mL/kg.

Brain Natriuretic Peptide

The relevance of BNP in identifying ventricular stretch has already been discussed. Its value in diagnosing heart failure is well-accepted. However, the development of interstitial edema as a result of PFB is almost always preceded by a stretch of the ventricular wall. Several studies have attempted to correlate BNP with the timing of onset of pulmonary edema. Studies have also attempted to identify the correlation between a fluid challenge and a unit change in BNP. Friesse et al. evaluated the profile of BNP as a marker of fluid resuscitation after injury.²⁴ This study was done at a trauma center. Age and sex of the patient did not seem to influence the BNP levels. This study demonstrated a correlation between a raise in BNP levels with the development of pulmonary edema on CXR. Patients who developed pulmonary edema had a mean BNP level of 110 pg/mL compared to 47 pg/mL among those who did not develop pulmonary edema. It may, therefore, be safer to moderate fluid therapy for patients

whose BNP crosses 100 pg/mL. In the study by Zhang et al.,¹⁴ Δ BNP was found to be a predictor of longer ICU and hospital stay amongst septic patients. An elevated BNP at admission was also associated with higher mortality. This study found a correlation of 10 pg/mL rise in BNP with a fluid challenge of 100 mL.

Ultrasonography

The benefits of a point of care USG for the assessment of a critically ill patient are well-known and have been alluded to earlier. Sonography provides two windows for identification of PFB: (i) the lung and (ii) the inferior vena cava (IVC). The presence of B lines on lung USG is a well-validated marker of presence of interstitial fluid. B lines have been shown to correlate well with EVLW and PAOP.^{25,26} It has been demonstrated that nonpredominance of B lines in the anterior chest could correlate with low PAOP.²⁶ Volpicelli et al. in a study including 73 patients attempted to compare lung USG predictability of EVLW versus PAOP.²⁷ They concluded that lung USG B profile predominance correlates well with pulmonary congestion indicated by EVLW, but not PAOP. This might argue more in favor of using EVLW to restrict fluids among susceptible patients. The results of this study might also suggest that PAOP <18 mmHg might not guarantee absence of cardiogenic pulmonary edema. An USG-scoring system has also been proposed to quantify the B profile pattern.²⁸ This system is shown in table 3. A very high degree of correlation was observed between the score and EVLW index. This scoring system identifies a score of >1.5 as being equal of an EVLW index >7 mL/kg. A score of >18.5 implied an EVLW index >15 mL/kg.

Inferior Vena Cava Assessment

Assessment of IVC is an accepted method of identifying fluid responders. However, a large absolute diameter of IVC >2.5 cm suggests a volume overload and no further fluids are likely to be beneficial. The point to note is that IVC distension is actually a sonographic equivalent of CVP. It can, therefore,

TABLE 3 Lung ultrasound scoring

Ultrasound finding	Score
No B line/intercostal space	0
One B line/intercostal space	1
Two B lines/intercostal space	2
Three B lines/intercostal space	3
Four B lines/intercostal space	4
Five B lines/intercostal space	5
Confluent B lines >50% intercostal space	6
Confluent B lines >75% intercostal space	7
Confluent B lines 100% intercostal space	8

be argued that the fallacies and drawbacks attributed to CVP might also apply to a distended IVC being treated as a marker of too much fluid.

HOW TO AVOID POSITIVE FLUID BALANCE AND FLUID OVERLOAD?

It is clear from the preceding discussion that PFB and FO are preventable causes of morbidity and mortality among critically ill patients. Some parameters have been identified as markers of FO. It is always advisable to prevent the genesis of PFB and FO rather than try to treat them later. The resuscitation-optimization-stabilization-evacuation schema seems to be a useful method in this direction. During the resuscitation phase, targeted volume therapy aiming to provide 30 mL of fluids per kilogram is an appropriate action, followed by a meticulously balanced decision making based on tendency for FO versus hemodynamic target achievement. During the optimization phase, effort should be made to strike a balance between the fluid balance and the markers of perfusion. Fluid restriction should begin in the stabilization phase to avoid a cumulative PFB. Maintenance fluids are better avoided at all stages. Markers like EVLW, BNP, and USG need to be employed at this stage. In the evacuation phase, PFB should be managed by pharmacological and extracorporeal means.

CONCLUSION

Positive fluid balance and FO are now established biomarkers of poor survival. Clinical examination alone does not suffice to prevent PFB. Extravascular lung water and BNP appear promising to guide therapy. Quantum of fluids also needs to be meticulously monitored and it is better to avoid PFB and FO rather than treat them.

REFERENCES

1. Benes J, Kirov M, Kuzkov V, et al. Fluid Therapy: Double-Edged Sword during Critical Care? *Biomed Res Int*. 2015;2015:729075.
2. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-75.
3. Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med*. 2005;33(8):1681-7.
4. Adesanya A, Rosero E, Timaran C, Clagett P, Johnston WE. Intraoperative fluid restriction predicts improved outcomes in major vascular surgery. *Vasc Endovascular Surg*. 2008;42(6):531-6.
5. Arlatti S, Storti E, Pradella V, et al. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. *Resuscitation*. 2007;72(3):371-8.
6. Ávila MO, Rocha PN, Zanetta DM, et al. Water balance, acute kidney injury and mortality of intensive care unit patients. *J Bras Nefrol*. 2014;36(3):379-88.
7. Besen BA, Gobatto AL, Melro LM, et al. Fluid and electrolyte overload in critically ill patients: An Overview. *World J Crit Care Med*. 2015;4(2):116-29.
8. Teboul JL, Monnet X. Detecting volume responsiveness and unresponsiveness in intensive care unit patients: two different problems, only one solution. *Crit Care*. 2009;13(4):175.
9. Paul EM. Hemodynamic Parameters to Guide Fluid Therapy. *Transfusion Alter Transfusion Med*. 2010;11(3):102-12.
10. Jozwiak M, Teboul JL, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. *Ann Intensive Care*. 2015;5(1):38.
11. Jozwiak M, Silva S, Persichini R, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. *Crit Care Med*. 2013;41(2):472-80.
12. Brown LM, Calfee CS, Howard JP, et al. Comparison of thermodilution measured extravascular lung water with chest radiographic assessment of pulmonary oedema in patients with acute lung injury. *Ann Intensive Care*. 2013;3(1):25.
13. Tagami T, Nakamura T, Kushimoto S, et al. Early-phase changes of extravascular lung water index as a prognostic indicator in acute respiratory distress syndrome patients. *Ann Intensive Care*. 2014;4:27.
14. Zhang Z, Zhang Z, et al. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resusc Emerg Med*. 2012;20:86.
15. Miglioranza MH, Gargani L, Sant'Anna RT, et al. Lung Ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging*. 2013;6(11):1141-51.
16. Lichtenstein D. FALLS-protocol: lung ultrasound in hemodynamic assessment of shock. *Heart Lung Vessel*. 2013;5(3):142-7.
17. Grissom CK, Hirshberg EL, Dickerson JB, et al. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. *Crit Care Med*. 2015;43(2):288-95.
18. Lee J, de Louw E, Niemi M, et al. Association between fluid balance and survival in critically ill patients. *J Intern Med*. 2014;277(4):468-77.
19. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, et al. An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. *Crit Care Med*. 2012;40(6):1753-60.
20. Pradeep A, Rajagopalam S, Kolli HK, et al. High volumes of intravenous fluid during cardiac surgery are associated with increased mortality. *HSR Proc Intensive Care Cardiovasc Anesth*. 2010;2(4):287-99.
21. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int*. 2009;76(4):422-7.
22. Chung FT, Lin SM, Lin SY, et al. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med*. 2008;102(7):956-61.
23. Pino-Sanchez F, Lara-Rosales R, Guerrero-López F, et al. Influence of extra-vascular lung water determination in fluid and vasoactive therapy. *J Trauma*. 2009;67(6):1220-4.
24. Friese RS, Dineen S, Jennings A, Pruitt J, McBride D, Shafi S, et al. Serum B-type natriuretic peptide: a marker of fluid resuscitation after injury? *J Trauma*. 2007;62(6):1346-51.
25. Agricola E, Bove T, Oppizzi M, et al. "Ultrasound comet-tail images": a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. *Chest*. 2005;127(5):1690-5.
26. Lichtenstein DA, Mezière GA, Lagoueyte JF, et al. A-lines and B-lines: Lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest*. 2009;136(4):1014-20.
27. Volpicelli G, Skurzak S, Boero E, et al. Lung ultrasound predicts well extravascular lung water but is of limited usefulness in the prediction of wedge pressure. *Anesthesiology*. 2014;121(2):320-7.
28. Enghard P, Rademacher S, Nee J, et al. Simplified lung ultrasound protocol shows excellent prediction of extravascular lung water in ventilated intensive care patients. *Crit Care*. 2015;19:36.

Blunt Chest Trauma

Mahesh Nirmalan, James Hanison

INTRODUCTION

Blunt chest trauma is a leading cause of hospital admissions and mortality worldwide. It represents between half and two-thirds of all chest trauma patients and the most common mechanism of injury is road traffic accident.^{1,2} The victims of blunt chest trauma are mostly younger males and the observed mortality rates may vary considerably ranging between 6 and 45%. This wide variation in the reported mortality figures reflects the differences in the initial impact, severity of injuries, effectiveness in prehospital care, and subsequent definitive medical treatment in emergency departments. In general, the evolution of signs and symptoms shows a very consistent pattern, reflecting the physiological consequences of the initial bony/soft tissue injuries and the (predictable) onset of secondary pulmonary complications, if these injuries are managed ineffectively or inadequately in the early stages. Therefore, the early management of blunt chest trauma has drawn considerable interest in recent years.

PATTERNS OF INJURY

Rib Fractures

Rib fractures are the most common injuries sustained following blunt chest.² It is estimated that approximately 10% of all trauma patients may sustain one or more rib fractures as part of their initial injury.³ Rib fractures may be associated with considerable pain, which renders breathing and coughing difficult and/or ineffective. They may also be associated with direct injury to the lung parenchyma causing contusions on the lung surface or frank hematomas within and around the lungs. These changes may impair ventilation or cause an increase in shunting, ventilation/perfusion mismatch, and/or dead-space ventilation. All of the above mechanisms may cause respiratory failure—characterized by hypoxemia, hypercarbia, labored breathing, and ineffective sputum clearance. Rib fractures also frequently lead to

delayed morbidity as a result of atelectasis and nosocomial infections that occur within collapsed or poorly ventilated alveolar units. These delayed complications are usually attributed to ineffective clearance of secretions associated with poor/ineffective cough and inadequate chest expansion during tidal breathing. As a result, approximately 6–10% of patients develop pneumonia and in 4% or so the infections are severe enough to cause death.⁴ The National Patient Safety Agency in the United Kingdom has identified these patients as “at-risk patients” to highlight the need for early recognition and careful monitoring within a high-care environment, where effective analgesia, physiotherapy, and controlled mobilization may be achieved in order to minimize the onset of these complications.⁵

In this context, some scoring systems have been developed, so that at-risk groups may be identified early and triaged to a high-care environment. Easter et al. developed a simple scoring system to assess the likelihood of developing complications following rib fracture⁶ where the total score was calculated on the basis of the number of fractures, whether or not the injury was unilateral or bilateral with an additional factor assigned to age, reflecting the fact that elderly patients were more prone to respiratory complications after injury.

Easter’s rib fracture score = (breaks × sides) + age factor

The allocated age factor was:

- Less than 50 years = 0
- 51–60 years = 1
- 61–70 years = 2
- 71–80 years = 3
- More than 80 years = 4.

It was suggested that patients with a higher score had a greater propensity to develop pulmonary complications and, therefore, greater length of stay in the hospital. The validity of this scoring system was evaluated by Maxwell et al. who found that, although higher scores were associated with a greater length of stay in intensive care unit (ICU) and hospital, the correlation between the variables was moderate-to-weak. Furthermore, the clinical usefulness of the score to guide

TABLE 1 Chest wall trauma scoring system

Age (years)	Number of rib fractures
• <45—1 point	• <3 breaks—1 point
• 45–65—2 points	• 3–5 breaks—2 points
• >65—3 points	• >5 breaks—3 points
Pulmonary contusion	Bilateral rib fractures
• None—0 points	• Unilateral fractures—0 points
• Mild—1 point	• Bilateral fractures—2 points
• Severe—2 points	
• Bilateral—3 points	
Total score: _____	

decision making, such as discharge to the ward or home, was also limited.⁷

Pressley et al. developed a more elaborate scoring system based on the number of fractures, age and the severity of lung contusions and this system is shown in table 1. This study found that patients with a cumulative score of >7 had a mortality of 14.3% compared to patients with scores of ≤6 who had a mortality of 4.2%. They also found that patients with lower scores were less likely to be mechanically ventilated, less likely to be admitted to ICU and had a shorter length of stay in hospital.⁸

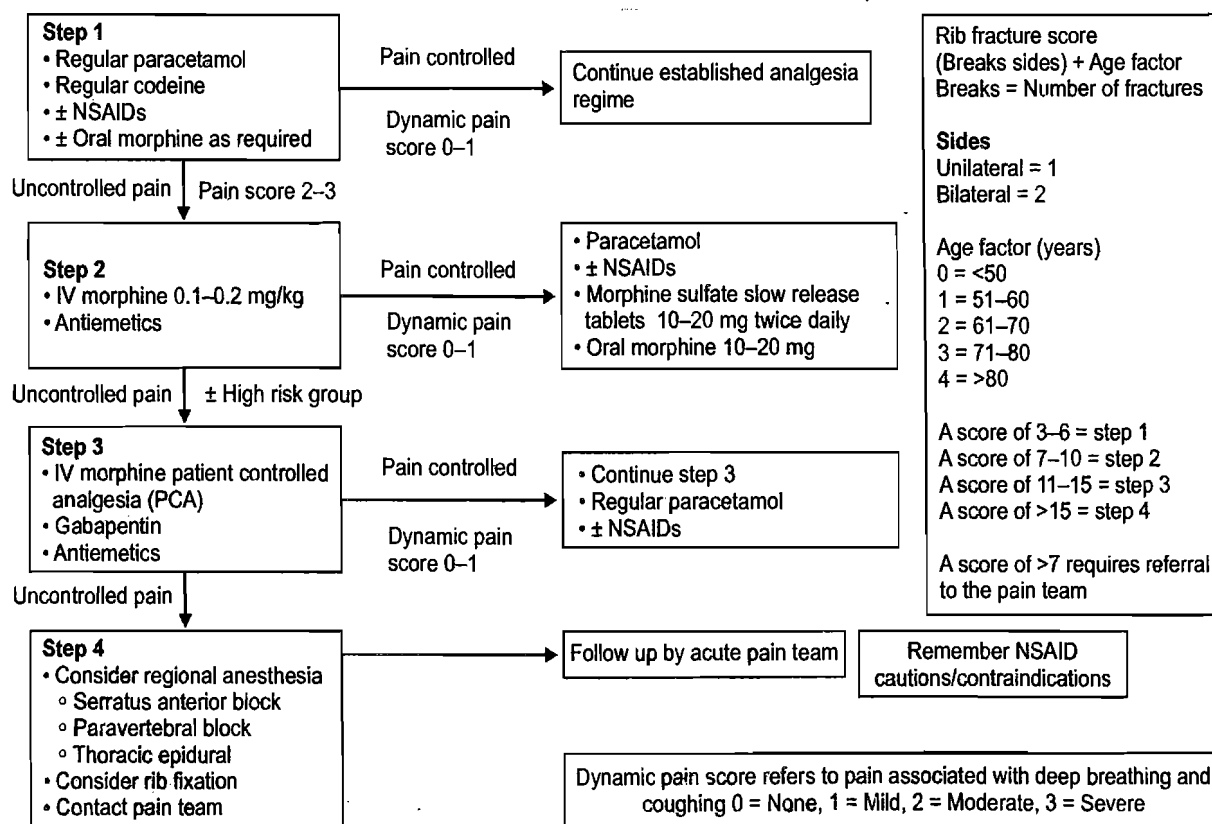
It is clear that both scoring systems are based on several arbitrary criteria and, hence, will lack sensitivity and

specificity when it comes to predicting clinical outcome in individual patients. Nevertheless, the usage of such systems will help to have a systematic approach to routine management of patients with rib fractures. This systematic approach is particularly useful to standardize the provision of analgesia and to set thresholds for the introduction of regional analgesic techniques at the early stages.

Analgesia for Rib Fracture

Several analgesia options are available including intravenous opioids (usually with a patient-controlled analgesia), nonnarcotic analgesics, and regional anesthetic techniques. May et al. have incorporated the Easter rib fracture score into an algorithm to guide the intensity of the multimodal analgesic regimen according to risk factors (Flowchart 1).⁹

Clinical trials suggest that effective thoracic epidural analgesia decreases the duration of mechanical ventilation, incidence of nosocomial pneumonia, and improves pulmonary function following rib fractures as compared to parenteral opioids alone.^{10,11} However, to date no mortality benefits have been demonstrated and this has led to a poor uptake of epidural blocks even in larger trauma centers. It must, however, be emphasized that in these patient groups the clinical trajectories determining death or survival are “sensitively dependent” on several factors that cannot be controlled for in clinical trials. Consequently, the absence of



IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

FLOWCHART 1: Multimodal analgesic regimen for rib fracture

“mortality benefits” must not be used as an argument to deny patients a treatment modality, such as epidural analgesia, that has been shown to have several short-term benefits including better quality of analgesia, reduced incidence of nosocomial infections, and decreased need for mechanical ventilation.¹² These short-term benefits are important and valid endpoints when it comes to assessing the effectiveness of thoracic epidural analgesia. Many patients may have contraindications to epidural analgesia, such as coagulopathy, and in such patients there is a need to consider other regional anesthetic techniques such as paravertebral blocks and serratus plane block. Both these techniques are amenable to continuous local anesthetic infusion via indwelling catheters, but require skilled personnel and appropriate equipment to provide them. Paravertebral block has been demonstrated as noninferior to epidural analgesia in terms of efficacy and preservation of pulmonary outcomes.¹³ Serratus plane block was first described in 2013 and as such has not entered common practice yet.¹⁴ Intrapleural and intercostal regional anesthetic techniques are, however, not recommended due to inferior safety and efficacy profiles.⁹

Overall, having a protocol-driven approach to analgesia, using a dedicated team whose members have a specialized interest in regional analgesic techniques and an objective scoring system to guide decision making is to be strongly recommended in the management of patients with multiple rib fractures.

Rib Fixation

Over the past few years, surgical plating technology has improved to the point of making surgical fixation of fractured ribs a viable option. There is increasing evidence that this is an appropriate treatment in selected patient groups. Marasco et al. evaluated the effect of surgical rib fixation for patients who were ventilator dependent with flail segment rib fractures. They found that surgical rib fixation reduced the length of stay on ICU and reduced the requirement for noninvasive ventilation (NIV) postextubation.¹⁵ Tanaka et al. also evaluated surgical rib fixation in ventilator-dependent patients and found a shorter duration of mechanical ventilation, shorter ICU stay, and improved pulmonary function tests at 12 months.¹⁶

The rib fixation technology has been assessed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom and they assert that rib fixation technology is safe and current evidence suggests benefit in selected patient groups. The NICE guidelines suggest that careful patient selection should be made by critical care specialists, chest physicians, and thoracic surgeons with appropriate experience.¹⁷ In particular, patients with more than four rib fractures, flail segments, and >45 years of age are currently considered suitable candidates for surgical rib fixation even though with greater experience and development of safer surgical techniques this list may expand in the future.

Injuries to Intrathoracic Viscera

The most common presentation following blunt thoracic trauma is a bony fracture of the thorax. However, many mechanisms of injury contain a considerable transfer of energy to the patient and injures to the heart, lungs, and associated structures must always be considered. Indeed, Shorr et al. noted that almost 25% of patients presenting with blunt chest trauma may have injuries to intrathoracic viscera in the absence of bony fractures.¹⁸ A high index of clinical suspicion coupled with trauma series computed tomography (CT) scan imaging is essential, if these intrathoracic injuries are not to be missed in the early stages.

Hemothorax

Hemothorax is the second most common injury after rib fractures following blunt chest trauma.² There is a wide spectrum of severity of hemothorax with some representing massive and persistent blood loss and some being more minor. Recent guidance suggests that all hemothoraces should be considered for insertion of an intercostal drain and if >1,500 mL of blood is drained then surgical exploration should be considered.¹⁹ They also suggest that persistent hemothorax following drain or a persistent air leak should trigger early surgical exploration in preference to repeated intercostal drain insertion.¹⁷

Pneumothorax

Pneumothorax is a frequent and serious complication following chest trauma. The intrapleural air can arise from laceration of the lung parenchyma by fractured ribs or by disruption of lung parenchyma by the forces and pressures generated at the time of the injury. Although the current British Thoracic Society guidelines for the management of spontaneous pneumothoraces suggest that some low-risk patients may be suitable for observation or needle aspiration,²⁰ the situation is different in trauma patients. Due to the dynamic and evolving nature of lung injury in the context of trauma, insertion of an intercostal drain should be considered in all trauma patients who have a pneumothorax at the time of initial presentation. While it is accepted practice to insert an intercostal drain for pneumothoraces that are large enough to be visible on chest X-ray (CXR), the correct approach for patients in whom a small pneumothorax is detected on a trauma series CT scan alone remains uncertain. It is recommended that such “occult” pneumothoraces may be considered for conservative management, unless they receive positive pressure ventilation.²¹

Pulmonary Contusion

Pulmonary contusion is a relatively frequent complication following blunt chest trauma. Pulmonary injury triggers an

inflammatory cascade that results in pulmonary infiltrates, reduced compliance, pulmonary hypertension, and impaired gas exchange. Pulmonary contusion in isolation does not carry a large risk of death with one study finding 100% survival after isolated pulmonary contusion.²² However, the appropriate fluid management strategy in patients with significant lung contusion remains controversial. The current evidence suggests that patients with pulmonary contusion should not be subjected to excessive fluid restriction. On the contrary they should be resuscitated as necessary with isotonic crystalloid (or colloid solution—depending on the overall hemodynamic picture) to achieve adequate tissue perfusion soon after injury. Once the usual resuscitation endpoints have been achieved, further fluid administration (usually in pursuit of an ambitious/erroneous level of urine output figure) should be meticulously avoided. Invasive hemodynamic monitoring techniques may aid in optimizing hemodynamic status while avoiding excessive fluid administration.

Patients with lung contusion and in need of respiratory support should be supported using a step-ladder approach involving positive end-expiratory pressure/continuous positive airway pressure, NIV, and mechanical ventilation using low-tidal volumes. In practical terms, the approach that should be adopted is no different to those with suspected acute lung injury and all attempts, including effective analgesia using regional techniques and minimal use of opiates/sedation should be employed to facilitate early weaning/extubation. Steroids, prophylactic antibiotics, or repeated bronchoalveolar lavages have no role in the management of lung contusions.

Diaphragmatic Rupture

Diaphragmatic injury is less frequent in blunt trauma as opposed to penetrating trauma, but is still present in 1–7% of cases. The left hemidiaphragm is most frequently affected with herniation of abdominal viscera into the thorax. Right hemidiaphragm rupture may be associated with major vessel disruption and associated high-morbidity risk. Bilateral rupture is rare.²³ Computed tomography imaging remains the modality of choice to detect diaphragmatic injuries. Chest X-ray has a low sensitivity, particularly in right-sided injuries where the liver may prevent herniation of abdominal viscera into the thorax.²⁴ Repair of diaphragmatic injury requires surgical treatment. Approach via laparotomy is most frequently performed, but thoracoscopic or combined approaches are also performed. Laparoscopic repair is also feasible.²⁵

Tracheobronchial Injury

Tracheobronchial injuries are an infrequent complication following blunt chest trauma. One study found that injuries occur most frequently to the bronchi within 2 cm of the

carina with right-sided injuries being more frequent, but left-sided injuries have better outcomes.²⁶ Another study found equal distribution of injuries throughout the trachea, carina, and bronchus.²⁷ Mortality is <10%.^{24,25}

Myocardial Contusion

Myocardial contusion is found to be present in approximately 10–20% of all admissions with blunt chest trauma. Abnormalities include ECG changes, elevated serum troponin, and regional wall motion abnormalities on echocardiography.²⁸ Although this seems to be a relatively frequently occurring event, the potential for long-term harm seems low.²⁹

Disruption of the Aorta

Injury to the thoracic aorta is an uncommon presentation following blunt chest trauma, but represents a significant risk of mortality. It is estimated to be present in <0.5% of cases. However, it has been demonstrated in approximately one-third of patients who die before arrival in hospital following road traffic accident.³⁰ The majority of patients, who do survive to hospital, have injuries that are located at the aortic isthmus. False aneurysm, dissection, and intimal tear may occur with false aneurysm being most frequent. In such patients, the presence of aortic injuries usually signify a high velocity injury and consequently as many as one-third of cases will die within 4 hours of hospital attendance, usually associated with multiple visceral injuries.

The Eastern Association for the Surgery of Trauma has made several recommendations for the investigation and management of aortic injury. They recommend contrast CT over the traditional aortic angiography, as the preferred method of imaging and endovascular repair in preference to open repair. They also recommend delayed repair over immediate repair as this planned approach is associated with reduced mortality.³¹ The Society for Vascular Surgery recommend endovascular repair for management of traumatic thoracic aortic injury as it is associated with reduced mortality, reduced renal injury, reduced cord ischemia, and reduced infection rates.³²

Cardiac Tamponade

Cardiac tamponade is most commonly associated with penetrating chest trauma.³³ It can also occur following blunt trauma, and when it does, the prognosis is grave. One case series found that all cases presenting with cardiac lacerations and tamponade in the context of blunt trauma died despite intervention.¹⁸ Emergency thoracotomy is rarely indicated in blunt thoracic trauma with chances of survival being very low following this intervention.³⁴

IMAGING MODALITIES

Computed Tomography

A review of trauma patients in Australia following blunt thoracic trauma found that CT was significantly more sensitive at detecting rib, sternum, and vertebral fractures as compared to CXR. It was also significantly more sensitive at detecting pneumothorax, hemopneumothorax, and lung contusion.³⁵ It was, however, noted that positive CT findings—not present on the conventional CXR, altered management in only 6% of patients following blunt chest trauma as the majority of small pneumothoraces and lung contusions did not require any specific interventions.³⁶ Patients with chest wall tenderness, reduced air entry, or abnormal respiratory effort were more likely to have additional findings detected on CT following a plain CXR.

The number of patients presenting with trauma is large and it is, therefore, necessary to select patients who should be subjected to CT scans. Current guidelines recommend that all patients who have sustained major trauma and multiple injuries should receive a CT scan from vertex of head to mid-thigh (the trauma CT).³⁷ Therefore, all patients with major multiple injuries will receive a CT. The decision, therefore, remains about which patients who have sustained isolated and minor chest injuries would benefit from a CT scan. Repeated clinical review and repeated observation of clinical signs of impending respiratory failure remain key to decision making in this context.

Lung Ultrasound

Ultrasonography of the chest has been increasing in popularity over the last two decades due to the increased availability, safety, and the potential for repeated bedside use. Protocolized scanning regimes have been developed such as the Bedside Lung Ultrasonography in Emergency (BLUE) protocol³⁸ for patients in critical care and the extended Focused Assessment with Sonography for Trauma (FAST) scan, which is specifically designed for use in trauma.³⁹ Thoracic ultrasound has a comparable specificity and a superior sensitivity compared to plain CXR.

Ultrasonography is a well-established modality of assessment in trauma patients with FAST scans routinely taught in Advanced Trauma Life Support (ATLS) courses. The inclusion of thoracic ultrasound is a sensible and feasible extension of this approach and may have the added benefit of detecting pneumothoraces not detected on plain CXR. Though not superior to CT, it may provide results more rapidly at the bedside.

Echocardiography

Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have been assessed in

the context of blunt chest trauma. Karalis et al. found that TTE provided suboptimal views in one in five patients with blunt chest trauma, whereas TEE was optimal in those. They found 30% of patients displayed myocardial contusions and this was predictive of developing cardiac complications, although only 4% of patients in total actually required treatment for cardiac complications.⁴⁰ Charillo et al. found that TTE was only possible in 38% of cases compared to 98% with TEE. They noted that TEE demonstrated 93% sensitivity in detecting aortic rupture.⁴¹ Transesophageal echocardiography has been demonstrated to have a superior sensitivity and equal specificity to helical chest CT in the detection of traumatic arterial injuries after blunt chest trauma. Transesophageal echocardiography also appears to be more sensitive at detecting myocardial contusions compared to CT.⁴²

Echocardiography appears to have a useful role in detecting arterial ruptures following blunt chest injury, at least as effectively as CT scan and TEE is more likely to provide consistently useful images in most patients. Echocardiography is more effective than CT at detecting myocardial injury although only a small proportion of these patients will go on to require treatment for cardiological complications.

SCORING SYSTEMS

Scoring systems, specific for rib fractures, have already been alluded to. A number of more generic scoring systems have also been developed to evaluate patients following blunt chest trauma of any kind (including all patients regardless of injury sustained). These scoring systems include the Pulmonary Contusion Score⁴³ and the Thoracic Trauma Severity Score (Table 2).⁴⁴

TABLE 2 Thoracic Trauma Severity Score

Age (years)	PaO₂ to FiO₂ ratio (mmHg/dL)
• <30—0 points	• >400—0 points
• 30–41—1 point	• 301–400—1 point
• 42–54—2 points	• 201–300—2 points
• 55–70—3 points	• 150–200—3 points
• >70—5 points	• <150—5 points
Pulmonary contusion	Pleural involvement
• None—0 points	• None—0 points
• 1 lobe unilateral—1 point	• Pneumothorax—1 point
• 1 lobe bilateral—2 points	• Unilateral hemothorax—2 points
• 2 lobes unilateral—3 points	• Bilateral hemothorax—3 points
• <2 lobes bilateral—4 points	• Tension pneumothorax—5 points
• >2 lobes bilateral—5 points	
Rib fractures	
• None—0 points	
• 1–3—1 point	
• 3–6 unilateral—2 points	
• >3 bilateral—3 points	
• Flail chest—5 points	
	Total score: _____

PaO₂, partial pressure arterial oxygen; FiO₂, fraction of inspired oxygen.

Mommsen et al. evaluated a number of scoring systems and compared them against established trauma scoring systems and found that the Thoracic Trauma Severity Score had superior sensitivity and specificity for predicting multiple organ dysfunction syndrome, acute respiratory distress syndrome (ARDS) and mortality.⁴⁵

LONG-TERM OUTCOME

Prolonged pulmonary morbidity, after the acute stages of the illness has revolved, has been reported in patients who sustained blunt chest trauma. Leone et al. found that patients had reduced exercise tolerance, altered pulmonary function tests and reduced quality of life at 6 months and 1 year on follow-up.⁴⁶ Whether this is a distinct disease entity or the sequelae of acute lung injury/ARDS itself remains to be elucidated.

CONCLUSION

Blunt chest trauma is a significant cause of morbidity and mortality and mainly affects young people. From the point of view of the general intensivists, the key management priorities should be focused around:

- Provision of effective analgesia using a standardized analgesic ladder guided by one of the objective rib fracture scoring systems within a high-care area where close hemodynamic monitoring is feasible
- Hemodynamic optimization using isotonic solutions and the avoidance of fluid over prescription once resuscitation targets have been achieved
- Step-ladder approach to respiratory support, including early weaning from mechanical ventilation
- Correct identification of patients who may benefit from surgical rib-fixation
- Complete and early characterization of nonbony/visceral injuries using appropriate imaging modalities.

The imaging modality of choice is the trauma CT, even though echocardiography and other ultrasound-based techniques are used increasingly. Scoring systems have a role in predicting outcome but should be used judiciously when determining the clinical trajectory in any individual patient.

REFERENCES

1. Demirhan R, Onan B, Oz K, Halezeroglu S. Comprehensive analysis of 4205 patients with chest trauma: a 10-year experience. *Interact Cardiovasc Thorac Surg.* 2009;9(3):450-3.
2. Khorsandi M, Skouras C, Prasad S, et al. Major cardiothoracic trauma: Eleven-year review of outcomes in the North West of England. *Ann R Coll Surg Engl.* 2015;97(4):298-303.
3. Flagel BT, Luchette FA, Reed RL, et al. Half-a-dozen ribs: the breakpoint for mortality. *Surgery.* 2005;138(4):717-23.
4. Brasel KJ, Guse CE, Layde P, et al. Rib fractures: relationship with pneumonia and mortality. *Crit Care Med.* 2006;34(6):1642-6.
5. National Health Service. (2011). Monitoring patients with fractured ribs. [online] Available from <http://www.nrls.npsa.nhs.uk/resources/?EntryId45=130182>. [Accessed September, 2016].
6. Easter A. Management of patients with multiple rib fractures. *Am J Crit Care.* 2001;10(5):320-7.
7. Maxwell CA, Mion LC, Dietrich MS. Hospitalized injured older adults: clinical utility of a rib fracture scoring system. *J Trauma Nurs.* 2012;19(3):168-74.
8. Pressley CM, Fry WR, Philp AS, et al. Predicting outcome of patients with chest wall injury. *Am J Surg.* 2012;204(6):910-3.
9. May L, Hillermann C, Patil S. Rib fracture management. *BJA Education.* 2015. Epublication ahead of print.
10. Bulger EM, Edwards T, Klotz P, et al. Epidural analgesia improves outcome after multiple rib fractures. *Surgery.* 2004;136(2):426-30.
11. Mackersie RC, Karagianes TG, Hoyt DB, et al. Prospective evaluation of epidural and intravenous administration of fentanyl for pain control and restoration of ventilatory function following multiple rib fractures. *J Trauma.* 1991;31(4):443-9.
12. Edwards D, Nirmalan M. Clinical trials in ventilator treatment: current perspectives and future challenges. *Curr Opin Crit Care.* 2010;16(1):34-8.
13. Mohta M, Verma P, Saxena AK, et al. Prospective, randomized comparison of continuous thoracic epidural and thoracic paravertebral infusion in patients with unilateral multiple fractured ribs—a pilot study. *J Trauma.* 2009;66(4):1096-101.
14. Blanco R, Parras T, McDonnell JG, et al. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. *Anaesthesia.* 2013;68(11):1107-13.
15. Marasco SF, Davies AR, Cooper J, et al. Prospective randomized controlled trial of operative rib fixation in traumatic flail chest. *J Am Coll Surg.* 2013;216(5):924-32.
16. Tanaka H, Yukioka T, Yamaguti Y, et al. Surgical stabilization of internal pneumatic stabilization? A prospective randomized study of management of severe flail chest patients. *J Trauma.* 2002;52(4):727-32.
17. National Institute for Health and Care Excellence. (2010). Insertion of metal rib reinforcements to stabilise a flail chest wall. [online] Available from <http://www.nice.org.uk/guidance/igp361/>. [Accessed September, 2016].
18. Shorr RM, Crittenden M, Indeck M, et al. Blunt thoracic trauma. Analysis of 515 patients. *Ann Surg.* 1987;206(2):200-5.
19. Mowery NT, Gunter OL, Collier BR, et al. Practice management guidelines for management of hemothorax and occult pneumothorax. *J Trauma.* 2011;70(2):510-8.
20. MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax.* 2010;65 Suppl 2:i18-31.
21. McGillicuddy D, Rosen P. Diagnostic dilemmas and current controversies in blunt chest trauma. *Emerg Med Clin North Am.* 2007;25(3):695-711.
22. Hoff SJ, Shotts SD, Eddy VA, et al. Outcome of isolated pulmonary contusion in blunt trauma patients. *Am Surg.* 1994;60(2):138-42.
23. Scharff JR, Naunheim KS. Traumatic diaphragmatic injuries. *Thorac Surg Clin.* 2007;17(1):81-5.
24. Gelman R, Mirvis SE, Gens D. Diaphragmatic rupture due to blunt trauma: sensitivity of plain chest radiographs. *AJR Am J Roentgenol.* 1991;156(1):51-7.
25. Bosanquet D, Farboud A, Luckraz H. A review diaphragmatic injury. *Respiratory Medicine CME.* 2009;2(1):1-6.
26. Kiser AC, O'Brien SM, Detterbeck FC. Blunt tracheobronchial injuries: treatment and outcomes. *Ann Thorac Surg.* 2001;71(6):2059-65.
27. Koletsis E, Prokakis C, Baltayiannis N, et al. Surgical decision making in tracheobronchial injuries on the basis of clinical evidences and the injury's anatomical setting: a retrospective analysis. *Injury.* 2012;43(9):1437-41.
28. Fulda GJ, Giberson F, Hailstone D, et al. An evaluation of serum troponin T and signal-averaged electrocardiography in predicting electrocardiographic abnormalities after blunt chest trauma. *J Trauma.* 1997;43(2):304-10.
29. Lindstaedt M, Gerding A, Lawo T, et al. Acute and long-term clinical significance of myocardial contusion following blunt thoracic trauma: results of a prospective study. *J Trauma.* 2002;52(3):479-85.
30. Demetriades D. Blunt thoracic aortic injuries: crossing the Rubicon. *J Am Coll Surg.* 2012;214(3):247-59.
31. Fox N, Schwartz D, Salazar JH, et al. Evaluation and management of blunt traumatic aortic injury: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2015;78(1):13S-46.

32. Lee WA, Matsumura JS, Mitchell RS, et al. Endovascular repair of traumatic thoracic aortic injury: clinical practice guidelines of the Society for Vascular Surgery. *J Vasc Surg*. 2011;53(1):187-92.
33. Henderson VJ, Smith RS, Fry WR, et al. Cardiac injuries: analysis of an unselected series of 251 cases. *J Trauma*. 1994;36(3):341-8.
34. Hunt PA, Greaves I, Owens WA. Emergency thoracotomy in thoracic trauma-a review. *Injury*. 2006;37(1):1-19.
35. Traub M, Stevenson M, McEvoy S, et al. The use of chest computed tomography versus chest X-ray in patients with major blunt trauma. *Injury*. 2007;38(1):43-7.
36. Marts B, Durham R, Shapiro M, Mazuski JE, et al. Computed tomography in the diagnosis of blunt thoracic injury. *Am J Surg*. 1994;168(6):688-92.
37. National Institute for Health and Care Excellence. (2016). Major trauma: assessment and initial management. [online] Available from: <http://www.nice.org.uk/guidance/ng39/>. [Accessed September, 2016].
38. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest*. 2008;134(1):117-25.
39. Kirkpatrick AW, Sirois M, Laupland KB, et al. Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: the Extended Focused Assessment with Sonography for Trauma (EFAST). *J Trauma*. 2004;57(2):288-95.
40. Karalis DG, Victor MF, Davis GA, et al. The role of echocardiography in blunt chest trauma: a transthoracic and transesophageal echocardiographic study. *J Trauma*. 1994;36(1):53-8.
41. Chirillo F, Totis O, Cavarzerani A, et al. Usefulness of transthoracic and transoesophageal echocardiography in recognition and management of cardiovascular injuries after blunt chest trauma. *Heart*. 1996;75(3):301-6.
42. Vignon P, Boncoeur MP, François B, et al. Comparison of multiplane transesophageal echocardiography and contrast-enhanced helical CT in the diagnosis of blunt traumatic cardiovascular injuries. *Anesthesiology*. 2001;94(4):615-22.
43. Tyburski JG, Collinge JD, Wilson RF, Eachempati SR. Pulmonary contusions: quantifying the lesions on chest X-ray films and the factors affecting prognosis. *J Trauma*. 1999;46(5):833-8.
44. Pape HC, Remmers D, Rice J, et al. Appraisal of early evaluation of blunt chest trauma: development of a standardized scoring system for initial clinical decision making. *J Trauma*. 2000;49(3):496-504.
45. Mommsen P, Zeckey C, Andruszkow H, et al. Comparison of different thoracic trauma scoring systems in regards to prediction of post-traumatic complications and outcome in blunt chest trauma. *J Surg Res*. 2012;176(1):239-47.
46. Leone M, Brégeon F, Antonini F, et al. Long-term outcome in chest trauma. *Anesthesiology*. 2008;109(5):864-71.

Guidelines for Cardiopulmonary Resuscitation: 2015 Update

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INTRODUCTION

The 2015 American Heart association (AHA) Guidelines Update for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC) are an update to the 2010 guidelines. This chapter will highlight the updates pertaining to adult patients only.

New AHA classification system for classes of recommendation and levels of evidence:

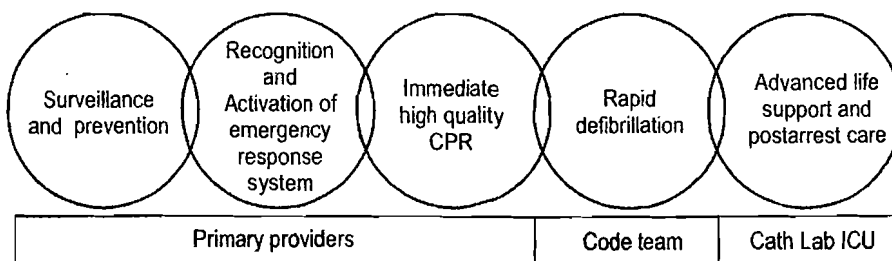
- Class I (strong): Benefit greatly exceeds the risk
- Class IIa (moderate): Benefit is greater than risk
- Class IIb (Weak): Benefit equal to or more than the risk

- Class III: No benefit
- Class III: Harm.

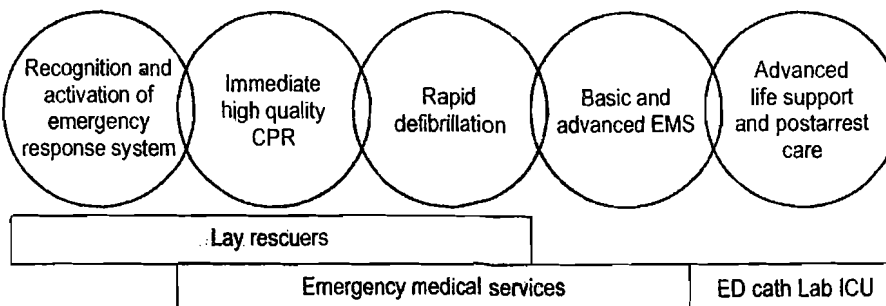
ADULT BASIC LIFE SUPPORT AND CARDIOPULMONARY RESUSCITATION

The 2015 guidelines update has made a distinction between in-hospital cardiac arrests (IHCAs) from out-of-hospital cardiac arrests (OHCAs) with two separate Chains of survival algorithm (Fig. 1). Adult basic life support (BLS) algorithm is given in flowchart 1.

Chain of survival in IHCA

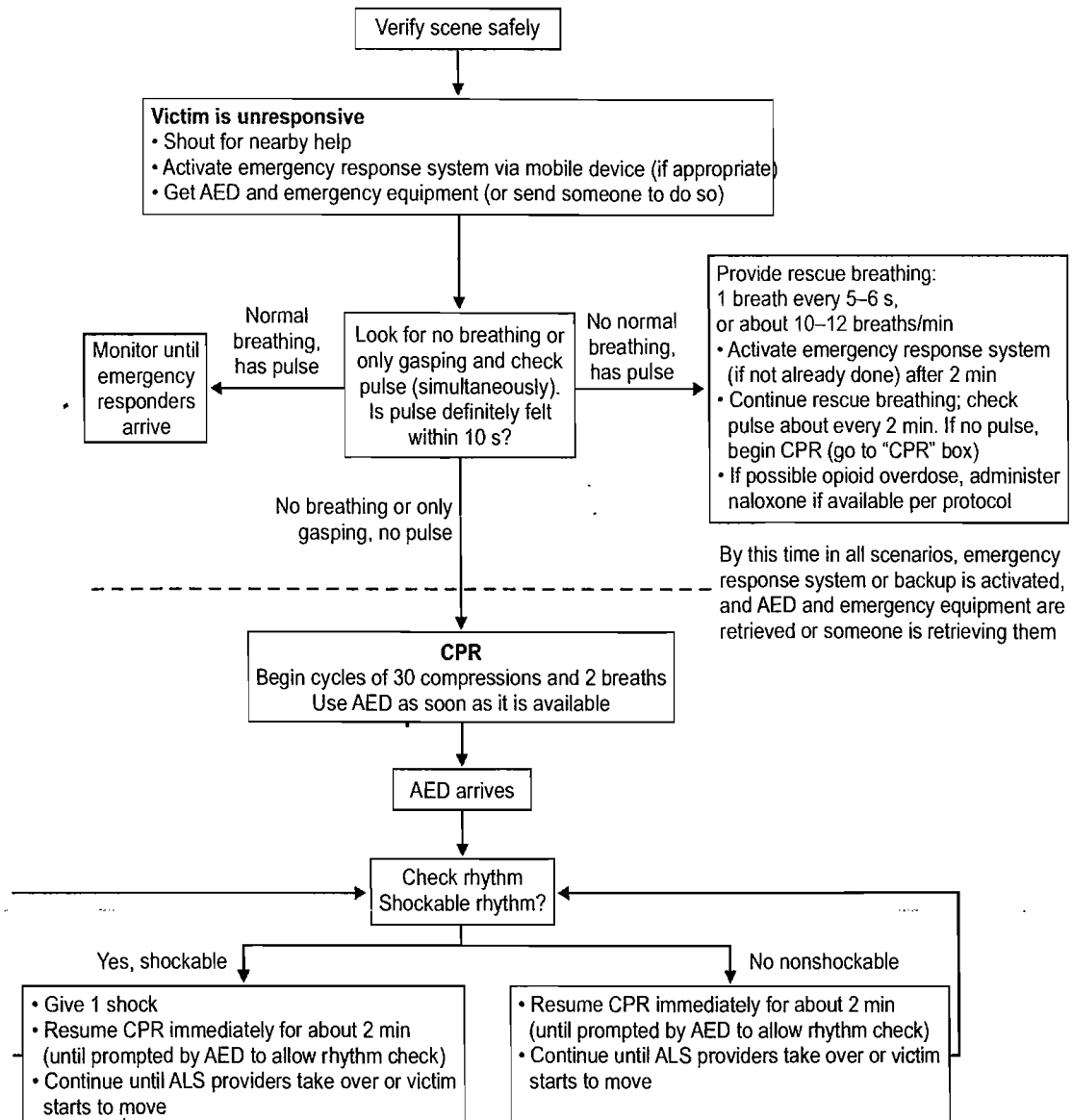


Chain of survival in OHCA



IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; EMS, emergency medical service.

FIG. 1: Chains of survival algorithm



CPR, cardiopulmonary resuscitation; ALS, advanced life support; AED, automated external defibrillator.

FLOWCHART 1: Basic life support algorithm

Untrained Lay Rescuer Cardiopulmonary Resuscitation

- Immediate recognition of unresponsiveness
- Activate emergency response system (if necessary through use of a mobile telephone) without leaving the victim
- Initiate CPR, if the unresponsive victim is not breathing or gasping
- Compression only CPR (CO-CPR) is recommended. Rationale: Lay rescuers are often reluctant to provide mouth-to-mouth respirations during CPR.¹⁻⁵ In adult victims, survival outcome was same for standard CPR and CO-CPR in multiple studies.⁶⁻¹⁰ Moreover, CO-CPR is easier to teach, learn, and perform, and it is more acceptable and likely to be performed by bystanders.^{9,11}

Positive pressure ventilation may be delayed for witnessed OHCA with a shockable rhythm. It is recommended to give three cycles of 200 continuous compressions may be given first, with passive oxygen insufflation, and positive-pressure ventilation may be delayed¹²⁻¹⁴

- Availability of public access defibrillator.

Suspected Opioid-related Life-threatening Emergency

Recommendations-

- For a patient with known or suspected opioid overdose and a respiratory arrest (but not cardiac arrest), intramuscular or intranasal naloxone may be given by trained rescuers, in addition to standard BLS measures (class IIa; New)

- For patients in cardiac arrest and if there is high suspicion for opiate overdose, naloxone may be given after initiation of CPR (class IIb; New)
- Persons at risk for opioid overdose may be provided education on how to respond to opioid overdose, and naloxone may be distributed (Class IIa) (New).

Rationale: As more death due to recreational as well as medicinal use of opioids are being reported, the administration of naloxone, in addition to standard BLS care, is an important element of resuscitation of patients with a known or suspected opioid overdose¹⁵⁻¹⁷

Chest Compressions

Recommendation

- Chest compressions should be performed at a rate of 100–120/min (class IIa; Updated)
Rationale: As rate increases beyond 120/min, depth decreases and the efficacy of chest compressions is reduced.^{18,19}
- Depth of compressions should be at least 2 inches or 5 cm for an average adult. Chest compression of more depth should be avoided (class I; Updated).
Rationale: Compression depth >6 cm may result in more injuries.²⁰⁻²⁶
- Avoid leaning on the victim's chest between compressions. This is in order to allow full chest wall recoil in between compressions (class IIa; Updated).
Rationale: Leaning on the chest wall between compressions prevents effective recoil and may decrease venous return with adverse hemodynamic consequences and potentially worse outcomes. It is also associated with decreased coronary perfusion.²⁶⁻²⁸
- Any pause in chest compression should be minimized before and after shock (class I; Updated).
- When an advanced airway is in place chest compressions should be paused for less than 10 seconds to deliver two breaths (class IIa; Updated)
- At least 60% of time should be spent on chest compression in between breaths (class IIb; New).
Rationale: A shorter duration of compression interruption is associated with higher likelihood of survival and return of spontaneous circulation (ROSC).²⁹⁻³⁴

Passive Oxygen versus Positive-pressure Oxygen during Cardiopulmonary Resuscitation

Recommendations

- Routine use of passive ventilation during conventional CPR is not recommended (class IIb; New).
- If a strategy of continuous chest compressions is being used, passive ventilation techniques with high-flow oxygen delivered via a face mask with an oropharyngeal airway may be considered as part of that strategy (class IIb; New).^{35,36}

Defibrillation

- For witnessed adult cardiac arrest, when an automated external defibrillator (AED) is immediately available, it should be used as soon as possible (class IIa; Updated)
- For adults with unmonitored cardiac arrest or when an AED is not immediately available, CPR should be started and continued till a defibrillator is available and ready for use (class IIa; Updated)
- In patients with unmonitored OHCA and an initial rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT), there is no benefit from a period of CPR of 90–180 seconds prior to defibrillation.³⁷⁻⁴³

Rationale: Prolonged VF may deplete the energy stores of the heart, and rapid defibrillation may be justified, regardless of the duration of arrest.

Analysis of Rhythm during Compressions

Use of artifact-filtering algorithms for analysis of electrocardiogram (ECG) rhythm during CPR is not recommended (class IIb; New).

ALTERNATIVE TECHNIQUES AND ANCILLARY DEVICES FOR CARDIOPULMONARY RESUSCITATION

Devices to Support Circulation

Recommendations

- Impedance threshold device (ITD) and active compression-decompression (ACD) device during CPR is not recommended to be used routinely (class III: No benefit; New)
Rationale: Three randomized controlled trials (RCTs) found no benefit to the use of ITD in patients with OHCA.⁴⁴⁻⁴⁶ Other trials with devices also showed no benefit.⁴⁷⁻⁴⁹ One RCT, the ResQ trial, showed improved neurologic function with the ACD – CPR + ITD, but there were limitations to that trial^{50,51}
- It may be used when equipment and properly trained personnel are available (class IIb; New)
- Mechanical chest compressions using a piston device, which is a compressed gas-driven or electrically powered device that delivers chest compression at set rate or load-distributing band devices (LDB-CPR), which encircles the chest though its circumference and is pneumatically or electrically actuated may be an alternative to manual chest compressions, if properly trained personnel are available and in situations like, prolonged CPR and CPR in a moving vehicle (class IIb; New).
Rationale: No definite benefit has been shown by these devices.⁵²⁻⁵⁴ However, they may be useful during prolonged CPR by trained personnel or when the CPR provider is fatigued.⁵⁵⁻⁵⁷

Extracorporeal Techniques and Invasive Perfusion Devices: Extracorporeal Cardiopulmonary Resuscitation

Recommendation

- For routine resuscitation, extracorporeal cardiopulmonary resuscitation (ECPR) is not recommended. Extracorporeal cardiopulmonary resuscitation refers to venoarterial extracorporeal membrane oxygenation during cardiac arrest. ECPR is resource intensive and costly, requiring quick vascular access, trained personnel, and specialized equipment. In carefully selected patients, it may be considered with a reversible etiology of cardiac arrest (class IIb; New)

Rationale: Data showing benefit of ECPR are case series that have included carefully selected patients with a few comorbidities, cardiac etiology of cardiac arrest and who received at least 10 minutes of conventional CPR without ROSC.⁵⁸⁻⁶⁰ Observational studies suggest a benefit in regard to survival and favorable neurologic outcome with the use of ECPR when compared with conventional CPR.⁶¹ There are currently no data from RCTs to support the use of ECPR for cardiac arrest in any setting.^{61,62}

ADULT ADVANCED CARDIOVASCULAR LIFE SUPPORT

Antiarrhythmic Drugs After Resuscitation⁶³⁻⁸⁹

Lignocaine

Recommendations

- Lignocaine may be given or continued immediately after ROSC, if cardiac arrest was due to VF/pVT (class IIb; New). Administration of prophylactic lidocaine during acute myocardial infarction is no longer advocated following studies that showed an increased incidence of asystole, bradycardia, and higher mortality with lignocaine prophylaxis
- Oral or intravenous β -blockers may be given early after hospitalization, if cardiac arrest was due to VF/pVT (class IIb New).

Vasopressors

Recommendation

- Epinephrine should be given as soon as possible after diagnosis of cardiac arrest with an initial nonshockable rhythm (class IIb; updated). High-dose epinephrine is not recommended for routine use in cardiac arrest (class III: No benefit; New)
Rationale: High-dose epinephrine achieves faster ROSC, but did not confer any advantage over standard dose epinephrine with respect to survival on hospital

discharge (SOHD) with a good neurologic recovery, or SOHD, or survival to hospital admission⁶⁷⁻⁷²

- Vasopressin should not be used instead of epinephrine in cardiac arrest (class IIb; Updated)

Rationale: Vasopressin was not found to have any advantage when used either as a substitute for multiple doses of epinephrine, or in combination with epinephrine in several trials. Outcomes assessed included ROSC, SOHD and neurological outcome.⁷⁴⁻⁷⁹ Vasopressin has, therefore, been removed from the adult cardiac arrest algorithm (Flowchart 2). Epinephrine should be given early after cardiac arrest in patients with nonshockable rhythms, but there is insufficient evidence for a similar recommendation in patients with shockable rhythms.⁸⁰⁻⁸⁵

Steroids

Recommendations

- In IHCA, the combination of intra-arrest vasopressin, epinephrine and methylprednisolone and postarrest hydrocortisone may be considered; however, further studies are needed before recommending the routine use of this therapeutic strategy (class IIb; New)

- For patients with OHCA, use of steroids during CPR is of uncertain benefit (class IIb; New)

Rationale: Two RCTs studying the use of a combination of methylprednisolone, vasopressin, and epinephrine during IHCA and hydrocortisone after ROSC for those with shock significantly improved ROSC, survival to hospital discharge, and good neurologic outcome compared with the use of only epinephrine and placebo.^{86,87} An RCT and an observational study using steroids as a sole treatment in OHCA did not improve survival to hospital discharge.^{88,89}

Management of Cardiac Arrest: Prognostication during Cardiopulmonary Resuscitation

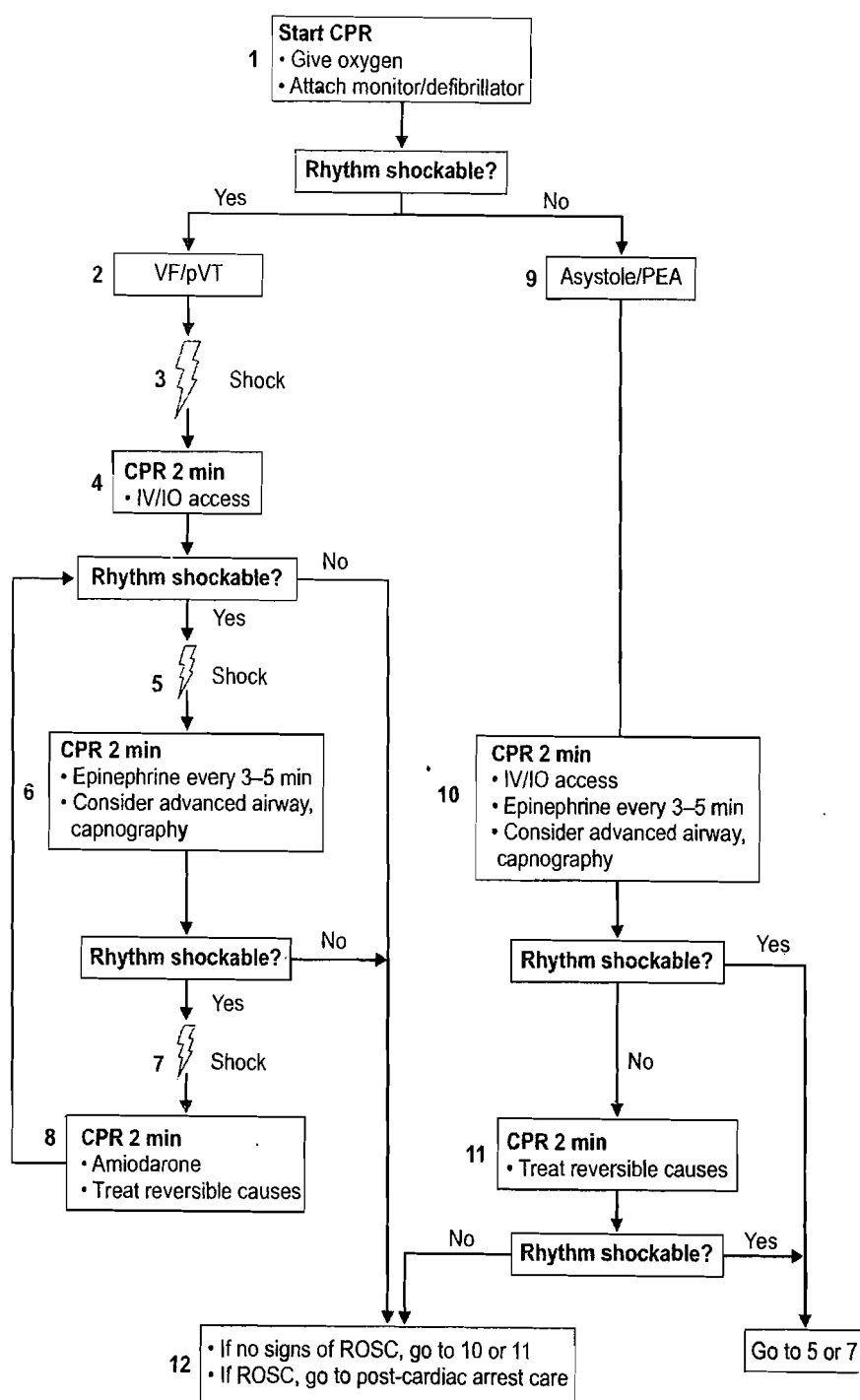
End-tidal Carbon Dioxide

Recommendations

- In intubated patients, failure to achieve an end-tidal Carbon Dioxide (EtCO_2) >10 mmHg after 20 minutes of CPR may be considered as one of the indicators to stop resuscitation. It should not be used in isolation (class IIb; New)

- In nonintubated patients, EtCO_2 should not be used in determining when to end resuscitative efforts (class III: Harm; New).

Rationale: Observational studies involving small numbers of patients suggest that EtCO_2 <10 mmHg after intubation and 20 minutes after CPR is associated with extremely low probability of ROSC and survival. However, these studies also have several confounding

**CPR quality**

- Push hard [at least 2 inches (5 cm)] and fast (100–120/min) and allow complete chest recoil
- Minimize interruption in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 min, or sooner if fatigued
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
 - If PETCO₂ <10 mmHg, attempt to improve CPR quality
- Intra-arterial pressure
 - If relaxation phase (diastolic) pressure <20 mmHg, attempt to improve CPR quality

Shock energy for defibrillation

- Biphasic: Manufacturer recommendation (e.g., initial dose of 120–200 J); if unknown, use maximum available. Second and subsequent dose should be equivalent, and higher doses may be considered
- Monophasic: 360 J

Drug therapy

- Epinephrine IV/IO dose: 1 mg every 3–5 min
- Amiodarone IV/IO dose: First dose: 300 mg bolus. Second dose: 150 mg

Advanced airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 s (10 breaths/min) with continuous chest compression

Return of spontaneous circulation

- Pulse and blood pressure
- Abrupt sustained increase in PETCO₂ (typically ≥40 mmHg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible causes

- Hypovolemia
- Hypoxia
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; PEA, pulseless electrical activity; IV, intravenous; IO, intraosseous; CPR, cardiopulmonary resuscitation

FLOWCHART 2: Adult cardiac arrest algorithm

factors. Hence, low EtCO₂ should not be the sole or major criterion to determine whether or not to terminate CPR.⁹⁰⁻⁹⁴

Postcardiac Arrest Care

Cardiovascular Care

Recommendations

- Emergent (not deferred or not at all) coronary angiography must be performed emergently (rather than later in the hospital stay or not at all) for OHCA patients with cardiac arrest of suspected cardiac etiology and ST elevation on ECG (class I; Updated)
- Emergent coronary angiography may be performed in selected (e.g., electrically or hemodynamically unstable) patients who are comatose after OHCA of suspected cardiac origin but without ST elevation on ECG (class IIa; Updated)
- Coronary angiography may be performed when indicated in postcardiac arrest patients even if the patient is comatose (class IIa; Updated)

Rationale: Several observational studies have shown that immediate coronary angiography in postcardiac arrest patients with ST elevation is associated with improved SOHD⁹⁵⁻¹⁰⁵ and improved neurological outcome associated.^{95-97,99,101-103} However, there are no prospective randomized trials evaluating these outcomes.

Hemodynamic Goals

Recommendation

- Any hypotension [systolic blood pressure <90 mmHg, mean arterial pressure (MAP) <65 mmHg] should be avoided and promptly treated (class IIb; New)
- Rationale: Identifying a universal, optimal MAP goal is difficult. However, patients having a systolic blood pressure of <90 mmHg or a mean arterial pressure of <65 have poor overall survival and poor neurological outcomes.¹⁰⁶⁻¹¹⁰

Temperature Management: Induced Hypothermia

Recommendations

- Patients with lack of meaningful response to verbal commands with ROSC after cardiac arrest have should receive targeted temperature management (TTM) (class I for VF/pVT OHCA; class I for non-VF/pVT—i.e., nonshockable—and in-hospital cardiac arrest; Updated)
- Temperature target between 32°C and 36°C should be selected and maintained constant (class I; Updated)
- Targeted temperature management should be maintained for at least 24 hours after achieving target temperature (class IIa; Updated)

- In the prehospital setting, routine cooling of patients after ROSC with rapid infusion of cold intravenous fluids is not recommended (class III; New)
- It may be reasonable to actively prevent fever in comatose patients after TTM (class IIb; New)

Rationale: Initial studies found that induced hypothermia (32°C and 34°C) resulted in better neurological outcomes compared to standard care. Another study found similar outcomes with temperature management at 36°C and at 33°C. Hence, TTM is beneficial, and clinicians can choose the temperature targets they wish to follow.¹¹¹⁻¹¹⁶ However, early initiation of cooling did not provide any benefit in randomized trials, and infusion of cold fluids in the prehospital period may result in more complications.¹¹⁷⁻¹²¹ Hyperthermia is associated with poor outcomes after cardiac arrest. It may be wise to prevent fever after TTM.¹²²⁻¹²⁹

Respiratory Care

Recommendations

- In order to avoid hypoxia after ROSC, the highest available oxygen concentration should be given until the arterial oxyhemoglobin saturation (SpO₂) or the PaO₂ can be measured (class IIa; New)
 - When resources to titrate the FiO₂ and to monitor SpO₂ are available, and the SpO₂ is 100%, the FiO₂ may be decreased to obtain a SaO₂ >94% (class IIa; Updated)
- Rationale: Hypoxia causes poor outcomes in postcardiac arrest victims. However, hyperoxia may also be detrimental.¹³⁰⁻¹³⁶ Hence, SpO₂ should be targeted to >94% at any point of time, and to avoid SpO₂ levels of 100%.

Prognostication of Outcome:

Timing of Outcome Prediction

Recommendations

- In patients with TTM, sedation, and/or paralysis, prognostication of neurological outcome based on clinical examination should be only done 72 hours after normothermia (class IIb; Updated)
 - In patients not treated with TTM, prognostication of neurological outcome based on clinical examination should be only done 72 hours after cardiac arrest (class I; New)
 - In case residual effects of sedation or paralysis are present, prognostication should be delayed even longer than 72 hours after cardiac arrest (class IIa; New)
- Rationale: The optimal time for prognostication is when the false-positive results (attributable to sedation, muscle relaxation and hypothermia) of the various prognostic tools approach zero. Multiple investigations suggest that it is necessary to wait to prognosticate for a minimum of 72 hours after ROSC to minimize the rate of false-positive

results in patients who had not undergone TTM and to wait for some period of time after return of normothermia for those using TTM.¹³⁷⁻¹⁴⁰

Prognosticators of Poor

Neurological Outcome: Clinical

Examination Findings that predict Outcome

Recommendations

- In comatose patients, who are not treated with TTM, the absence of pupillary reflex to light at 72 hours or more after cardiac arrest [false-positive rate (FPR), 0%; 95% confidence interval (CI), 0–8%; class IIa; New]
- In comatose patients, who are treated with TTM, the absence of pupillary reflex to light at 72 hours or more after cardiac arrest (FPR, 1%; 5% CI, 0–3%; class I; New)
- The presence of status myoclonus during the first 72–120 hours after cardiac arrest along with other diagnostic tests at 72 or more hours after cardiac arrest (class IIa; New)
- The motor examination may be a reasonable means to identify the population who need further prognostic testing to predict poor outcome (class IIb; new)

The following should not be used to predict neurological outcome:

- Absent motor movements or extensor posturing should not be used alone for predicting a poor neurologic outcome (FPR, 10%; 95% CI, 7–15% to FPR, 15%; 95% CI, 5–31%; class III: harm; New)
- The presence of myoclonus, which is distinct from status myoclonus, should not be used to predict poor neurologic outcomes (class III: harm; Updated).

Prognostication of Outcome:

Imaging Tests to predict Outcome

Recommendations

- In patients, who are comatose after resuscitation from cardiac arrest and not treated with TTM, presence of a marked reduction of the gray-white ratio on brain computed tomography (CT) obtained within 2 hours after cardiac arrest to predict poor outcome (class IIb, level of evidence B—nonrandomized; New)
- Extensive restriction of diffusion on brain magnetic resonance imaging (MRI) at 2–6 days after cardiac arrest in combination with other established predictors (class IIb, level of evidence B—nonrandomized; New).

Recommendations

- Blood levels of neuron-specific enolase (NSE) and S-100B should not be used alone to predict a poor neurologic outcome (class III: Harm; Updated)
- High-serum values of NSE at 48–72 hours after cardiac arrest support the prognosis of a poor neurologic outcome when performed with other prognostic tests (class IIb),

and especially if repeated sampling reveals persistently high values at 72 hours or more after cardiac arrest.

CONCLUSION

The field of cardiopulmonary resuscitation is ever evolving. The 2015 guidelines have made a clear distinction in the chains of survival of OHCA and IHCA. These guidelines have also made changes in the rate and depth of compressions, and recommendations regarding decreased leaning and importance of compression-only CPR. There is no role of vasopressin and high dose adrenaline. The role of coronary angiography has been better defined in post cardiac arrest care. The guidelines recommend targeted temperature management as a modality to manage comatose survivors with wide range of target temperature from 32 to 36 degree centigrade. Knowledge of predictors of poor outcome and thus prognostication translates into optimal care and resource use.

REFERENCES

1. SOS-KANTO Study Group. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet*. 2007;369:920-6.
2. Vaillancourt C, Stiell IG, Wells GA. Understanding and improving low bystander CPR rates: a systematic review of the literature. *CJEM*. 2008;10:51-65.
3. Coons SJ, Guy MC. Performing bystander CPR for sudden cardiac arrest: behavioral intentions among the general adult population in Arizona. *Resuscitation*. 2009;80:334-40.
4. Becker LB, Berg RA, Pepe PE, et al. A reappraisal of mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation: a statement for healthcare professionals from the Ventilation Working Group of the Basic Life Support and Pediatric Life Support Subcommittees, American Heart Association. *Circulation*. 1997;96:2102-12.
5. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation*. 2007;116:2900-7.
6. Hüpfel M, Selig HF, Nagele P. Chest-compression-only versus standard cardiopulmonary resuscitation: a meta-analysis. *Lancet*. 2010;376:1552-7.
7. Kitamura T, Iwami T, Kawamura T, et al. Implementation Working Group for All-Japan Utstein Registry of the Fire and Disaster Management Agency. Bystander-initiated rescue breathing for out-of-hospital cardiac arrests of noncardiac origin. *Circulation*. 2010;122:293-9.
8. Kitamura T, Iwami T, Kawamura T, et al. Time-dependent effectiveness of chest compression-only and conventional cardiopulmonary resuscitation for out-of-hospital cardiac arrest of cardiac origin. *Resuscitation*. 2011;82:3-9.
9. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA*. 2010;304:1447-54.
10. Panchal AR, Bobrow BJ, Spaite DW, et al. Chest compression-only cardiopulmonary resuscitation performed by lay rescuers for adult out-of-hospital cardiac arrest due to non-cardiac aetiologies. *Resuscitation*. 2013;84:435-9.
11. Sayre MR, Berg RA, Cave DM, et al. American Heart Association Emergency Cardiovascular Care Committee. Hands-only (compression-only) cardiopulmonary resuscitation: a call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest: a science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. *Circulation*. 2008;117:2162-7.
12. Mccsler J, Itty A, Sanders A, et al. Cardiocerebral resuscitation is associated with improved survival and neurologic outcome from out-of-hospital cardiac arrest in elders. *Acad Emerg Med*. 2010;17:269-75.

13. Bobrow BJ, Ewy GA, Clark L, et al. Passive oxygen insufflation is superior to bag-valve-mask ventilation for witnessed ventricular fibrillation out-of-hospital cardiac arrest. *Ann Emerg Med*. 2009;54:656-62.e1.
14. Kellum MJ, Kennedy KW, Barney R, et al. Cardiocerebral resuscitation improves neurologically intact survival of patients with out-of-hospital cardiac arrest. *Ann Emerg Med*. 2008;52:244-52.
15. Watley AY, Doe-Simkins M, Quinn E, et al. Opioid overdose prevention with intranasal naloxone among people who take methadone. *J Subst Abuse Treat*. 2013;44:241-7.
16. Albert S, Brason FW 2nd, Sanford CK, et al. Community-based overdose prevention in rural North Carolina. *Pain Med*. 2011;12:S77-85.
17. Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. *J Addict Dis*. 2006;25:89-96.
18. Idris AH, Guffey D, Pepe PE, et al. Resuscitation Outcomes Consortium Investigators. Chest compression rates and survival following out-of-hospital cardiac arrest. *Crit Care Med*. 2015;43:840-8.
19. Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. *Circulation*. 2012;125:3004-12.
20. Vadeboncoeur T, Stolz U, Panchal A, et al. Chest compression depth and survival in out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:182-8.
21. Hostler D, Everson-Stewart S, Rea TD, et al. Resuscitation Outcomes Consortium Investigators. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. *BMJ*. 2011;342:d512.
22. Stiell IG, Brown SP, Christenson J, et al. What is the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? *Crit Care Med*. 2012;40:1192-8.
23. Stiell IG, Brown SP, Nichol G; Resuscitation Outcomes Consortium Investigators. What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients? *Circulation*. 2014;130:1962-70.
24. Bohn A, Weber TP, Wecker S. The addition of voice prompts to audiovisual feedback and debriefing does not modify CPR quality or outcomes in out of hospital cardiac arrest—a prospective, randomized trial. *Resuscitation*. 2011;82:257-62.
25. Hellevuo H, Sainio M, Nevalainen R, et al. Deeper chest compression—more complications for cardiac arrest patients? *Resuscitation*. 2013;84:760-5.
26. Zuercher M, Hilwig RW, Ranger-Moore J, et al. Leaning during chest compressions impairs cardiac output and left ventricular myocardial blood flow in piglet cardiac arrest. *Crit Care Med*. 2010;38:1141-6.
27. Niles DE, Sutton RM, Nadkarni VM, et al. Prevalence and hemodynamic effects of leaning during CPR. *Resuscitation*. 2011;82:S23-6.
28. Fried DA, Leary M, Smith DA, et al. The prevalence of chest compression leaning during in-hospital cardiopulmonary resuscitation. *Resuscitation*. 2011;82:1019-24.
29. Sell RE, Sarno R, Lawrence B, et al. Minimizing pre- and post-defibrillation pauses increases the likelihood of return of spontaneous circulation (ROSC). *Resuscitation*. 2010;81:822-5.
30. Cheskes S, Schmicker RH, Christenson J, et al. Perishock pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. *Circulation*. 2011;124:58-66.
31. Cheskes S, Schmicker RH, Verbeek PR, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014;85:336-42.
32. Vaillancourt C, Everson-Stewart S, Christenson J, et al. The impact of increased chest compression fraction on return of spontaneous circulation for out-of-hospital cardiac arrest patients not in ventricular fibrillation. *Resuscitation*. 2011;82:1501-7.
33. Jost D, Degrange H, Verret C, et al. DEF 2005: a randomized controlled trial of the effect of automated external defibrillator cardiopulmonary resuscitation protocol on outcome from out-of-hospital cardiac arrest. *Circulation*. 2010;121:1614-22.
34. Beesems SG, Wijmans L, Tijssen JG, Koster RW. Duration of ventilations during cardiopulmonary resuscitation by lay rescuers and first responders: relationship between delivering chest compressions and outcomes. *Circulation*. 2013;127:1585-90.
35. Saissy JM, Boussignac G, Cheptel E, et al. Efficacy of continuous insufflations of oxygen combined with active cardiac compression-decompression during out-of-hospital cardiorespiratory arrest. *Anesthesiology*. 2000;92:1523-30.
36. Bertrand C, Hemery F, Carli P, et al. Constant flow insufflation of oxygen as the sole mode of ventilation during out-of-hospital cardiac arrest. *Intensive Care Med*. 2006;32:843-51.
37. Stiell IG, Nichol G, Leroux BG, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:787-97.
38. Ma MH, Chiang WC, Ko PC, et al. A randomized trial of compression first or analyze first strategies in patients with out-of-hospital cardiac arrest: results from an Asian community. *Resuscitation*. 2012;83:806-12.
39. Koike S, Tanabe S, Ogawa T, et al. Immediate defibrillation or defibrillation after cardiopulmonary resuscitation. *Prehosp Emerg Care*. 2011;15:393-400.
40. Meier P, Baker P, Jost D, et al. Chest compressions before defibrillation for out-of-hospital cardiac arrest: a meta-analysis of randomized controlled clinical trials. *BMC Med*. 2010;8:52.
41. Simpson PM, Goodger MS, Bendall JC. Delayed versus immediate defibrillation for out-of-hospital cardiac arrest due to ventricular fibrillation: A systematic review and meta-analysis of randomised controlled trials. *Resuscitation*. 2010;81:925-31.
42. Huang Y, He Q, Yang LJ, et al. Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest. *Cochrane Database Syst Rev*. 2014;9:CD009803.
43. Rea T, Prince D, Morrison L, et al. Association between survival and early versus later rhythm analysis in out-of-hospital cardiac arrest: do agency-level factors influence outcomes? *Ann Emerg Med*. 2014;64:1-8.
44. Pirralo RG, Aufderheide TP, Provo TA, et al. Effect of an inspiratory impedance threshold device on hemodynamics during conventional manual cardiopulmonary resuscitation. *Resuscitation*. 2005;66:13-20.
45. Aufderheide TP, Pirralo RG, Provo TA, et al. Clinical evaluation of an inspiratory impedance threshold device during standard cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest. *Crit Care Med*. 2005;33:734-40.
46. Aufderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med*. 2011;365:798-806.
47. Plaisance P, Lurie KG, Payen D. Inspiratory impedance during active compression-decompression cardiopulmonary resuscitation: a randomized evaluation in patients in cardiac arrest. *Circulation*. 2000;101:989-94.
48. Plaisance P, Lurie KG, Vicaut E, et al. Evaluation of an impedance threshold device in patients receiving active compression-decompression cardiopulmonary resuscitation for out of hospital cardiac arrest. *Resuscitation*. 2004;61:265-71.
49. Wolcke BB, Mauer DK, Schoefmann MF, et al. Comparison of standard cardiopulmonary resuscitation versus the combination of active compression-decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. *Circulation*. 2003;108:2201-5.
50. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. *Lancet*. 2011;377:301-11.
51. Frascone RJ, Wayne MA, Swor RA, et al. Treatment of non-traumatic out-of-hospital cardiac arrest with active compression decompression cardiopulmonary resuscitation plus an impedance threshold device. *Resuscitation*. 2013;84:1214-22.
52. Smekal D, Johansson J, Huzevka T, et al. A pilot study of mechanical chest compressions with the LUCAS™ device in cardiopulmonary resuscitation. *Resuscitation*. 2011;82:702-6.
53. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet*. 2015;385:947-55.
54. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA*. 2014;311:53-61.

55. Steinmetz J, Barnung S, Nielsen SL, et al. Improved survival after an out-of-hospital cardiac arrest using new guidelines. *Acta Anaesthesiol Scand*. 2008;52:908-13.
56. Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *JAMA*. 2006;295:2620-8.
57. Wik L, Olsen JA, Persse D, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. *Resuscitation*. 2014;85:741-8.
58. Shin TG, Choi JH, Jo IJ, et al. Extracorporeal cardiopulmonary resuscitation in patients with in-hospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation. *Crit Care Med*. 2011;39:1-7.
59. Maekawa K, Tanno K, Hase M, et al. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med*. 2013;41:1186-96.
60. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation*. 2014;85:762-8.
61. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet*. 2008;372:554-61.
62. Huang SC, Wu ET, Chen YS, et al. Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. *Crit Care Med*. 2008;36:1607-13.
63. Skrifvars MB, Pettilä V, Rosenberg PH, et al. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation*. 2003;59:319-28.
64. Sadowski ZP, Alexander JH, Skrabucha B, et al. Multicenter randomized trial and a systematic overview of lidocaine in acute myocardial infarction. *Am Heart J*. 1999;137:792-8.
65. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA*. 1993;270:1589-95.
66. Kudenchuk PJ, Newell C, White L, et al. Prophylactic lidocaine for post resuscitation care of patients with out-of-hospital ventricular fibrillation cardiac arrest. *Resuscitation*. 2013;84:1512-8.
67. Callahan M, Madsen CD, Barton CW, et al. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA*. 1992;268:2667-72.
68. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. *N Engl J Med*. 1998;339:1595-601.
69. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group. *N Engl J Med*. 1992;327:1051-5.
70. Sherman BW, Munger MA, Foulke GE, et al. High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy. *Pharmacotherapy*. 1997;17:242-7.
71. Stiell IG, Hebert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. *N Engl J Med*. 1992;327:1045-50.
72. Choux C, Gueugniaud PY, Barbicux A, et al. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. *Resuscitation*. 1995;29:3-9.
73. Mukoyama T, Kinoshita K, Nagao K, et al. Reduced effectiveness of vasopressin in repeated doses for patients undergoing prolonged cardiopulmonary resuscitation. *Resuscitation*. 2009;80:755-61.
74. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med*. 2008;359:21-30.
75. Ong ME, Tiah L, Leong BS, et al. A randomised, double-blind, multi-centre trial comparing vasopressin and adrenaline in patients with cardiac arrest presenting to or in the Emergency Department. *Resuscitation*. 2012;83:953-60.
76. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med*. 2004;350:105-13.
77. Ducros L, Vicaut E, Soleil C, et al. Effect of the addition of vasopressin or vasopressin plus nitroglycerin to epinephrine on arterial blood pressure during cardiopulmonary resuscitation in humans. *J Emerg Med*. 2011;41:453-9.
78. Lindher KH, Dirks B, Strohmenger HU, et al. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet*. 1997;349:535-7.
79. Callaway CW, Hostler D, Doshi AA, et al. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol*. 2006;98:1316-21.
80. Donnino MW, Saliccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ*. 2014;348:g3028.
81. Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: an observational cohort study. *Crit Care*. 2013;17:R188.
82. Nakahara S, Tomio J, Nishida M, et al. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med*. 2012;19:782-92.
83. Kosciak C, Pinawin A, McGovern H, et al. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:915-20.
84. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. *Circ J*. 2012;76:1639-45.
85. Cantrell CL Jr, Hubble MW, Richards ME. Impact of delayed and infrequent administration of vasopressors on return of spontaneous circulation during out-of-hospital cardiac arrest. *Prehosp Emerg Care*. 2013;17:15-22.
86. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med*. 2009;169:15-24.
87. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2013;310:270-9.
88. Paris PM, Stewart RD, Degler F. Prehospital use of dexamethasone in pulseless idioventricular rhythm. *Ann Emerg Med*. 1984;13:1008-10.
89. Tsai MS, Huang CH, Chang WT, et al. The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. *Am J Emerg Med*. 2007;25:318-25.
90. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;337:301-6.
91. Wayne MA, Levine RL, Miller CC. Use of end-tidal carbon dioxide to predict outcome in prehospital cardiac arrest. *Ann Emerg Med*. 1995;25:762-7.
92. Callahan M, Barton C. Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. *Crit Care Med*. 1990;18:358-62.
93. Cantineau JP, Lambert Y, Merckx P, et al. End-tidal carbon dioxide during cardiopulmonary resuscitation in humans presenting mostly with asystole: a predictor of outcome. *Crit Care Med*. 1996;24:791-6.
94. Ahrens T, Schalkom L, Bettorf K, et al. End-tidal carbon dioxide measurements as a prognostic indicator of outcome in cardiac arrest. *Am J Crit Care*. 2001;10:391-8.
95. Hollenbeck RD, McPherson JA, Mooney MR, et al. Early cardiac catheterization is associated with improved survival in comatose survivors of cardiac arrest without STEMI. *Resuscitation*. 2014;85:88-95.
96. Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. *Circulation*. 2011;124:206-14.
97. Gräsner JT, Meybohm P, Lefering R, et al. ROSC after cardiac arrest—the RACA score to predict outcome after out-of-hospital cardiac arrest. *Eur Heart J*. 2011;32:1649-56.

98. Cronier P, Vignon P, Bouferrache K, et al. Impact of routine percutaneous coronary intervention after out-of-hospital cardiac arrest due to ventricular fibrillation. *Crit Care*. 2011;15:R122.
99. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? *Eur Heart J Acute Cardiovasc Care*. 2012;1:291-301.
100. Aurore A, Jabre P, Liot P, et al. Predictive factors for positive coronary angiography in out-of-hospital cardiac arrest patients. *Eur J Emerg Med*. 2011;18:73-6.
101. Nanjappa VB, Nayyar V. Immediate coronary angiogram in comatose survivors of out-of-hospital cardiac arrest—an Australian study. *Resuscitation*. 2012;83:699-704.
102. Strote JA, Maynard C, Olsufka M, et al. Comparison of role of early (less than six hours) to later (more than six hours) or no cardiac catheterization after resuscitation from out-of-hospital cardiac arrest. *Am J Cardiol*. 2012;109:451-4.
103. Tømte O, Andersen GØ, Jacobsen D, et al. Strong and weak aspects of an established post-resuscitation treatment protocol-A five-year observational study. *Resuscitation*. 2011;82:1186-93.
104. Waldo SW, Armstrong EJ, Kulkarni A, et al. Comparison of clinical characteristics and outcomes of cardiac arrest survivors having versus not having coronary angiography. *Am J Cardiol*. 2013;111:1253-8.
105. Zanuttini D, Armellini I, Nucifora G, et al. Impact of emergency coronary angiography on in-hospital outcome of unconscious survivors after out-of-hospital cardiac arrest. *Am J Cardiol*. 2012;110:1723-8.
106. Beylin ME, Perman SM, Abella BS, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. *Intensive Care Med*. 2013;39:1981-8.
107. Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2009;80:418-24.
108. Laurent I, Monchi M, Chiche JD, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2002;40:2110-6.
109. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73:29-39.
110. Walters EL, Morawski K, Dorotta I, et al. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-of-hospital cardiac arrest: a feasibility study. *Shock*. 2011;35:360-6.
111. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. *Circulation*. 2011;123:877-86.
112. Testori C, Sterz F, Behringer W, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation*. 2011;82:1162-7.
113. Vaahersalo J, Hiltunen P, Tiainen M, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med*. 2013;39:826-37.
114. Mader TJ, Nathanson BH, Soares WE 3rd, et al. Comparative Effectiveness of Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest: Insight from a Large Data Registry. *Ther Hypothermia Temp Manag*. 2014;4:21-31.
115. Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? *Resuscitation*. 2013;84:620-5.
116. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369:2197-206.
117. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation*. 2010;122:737-42.
118. Bernard SA, Smith K, Cameron P, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. *Crit Care Med*. 2012;40:747-53.
119. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA*. 2014;311:45-52.
120. Debatty G, Maignan M, Savary D, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. *Intensive Care Med*. 2014;40:1832-42.
121. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation*. 2010;122:729-36.
122. Gebhardt K, Guyette FX, Doshi AA, et al. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation*. 2013;84:1062-7.
123. Aldhoun B, Melenovsky V, Kautzner J. Clinical predictors of outcome in survivors of out-of-hospital cardiac arrest treated with hypothermia. *Cor et Vasa*. 2012;54:e68-75.
124. Benz-Woerner J, Delodder F, Benz R, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. *Resuscitation*. 2012;83:338-42.
125. Bouwes A, Robillard LB, Binnekade JM, et al. The influence of rewarming after therapeutic hypothermia on outcome after cardiac arrest. *Resuscitation*. 2012;83:996-1000.
126. Leary M, Grossestreuer AV, Iannacone S, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. *Resuscitation*. 2013;84:1056-61.
127. Cocchi MN, Boone MD, Giberson B, et al. Fever after rewarming: incidence of pyrexia in postcardiac arrest patients who have undergone mild therapeutic hypothermia. *J Intensive Care Med*. 2014;29:365-9.
128. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. *Resuscitation*. 2013;84:1734-40.
129. Winters SA, Wolf KH, Kettinger SA, et al. Assessment of risk factors for post-rewarming "rebound hyperthermia" in cardiac arrest patients undergoing therapeutic hypothermia. *Resuscitation*. 2013;84:1245-9.
130. Janz DR, Hollenbeck RD, Pollock JS, et al. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest. *Crit Care Med*. 2012;40:3135-9.
131. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303:2165-71.
132. Elmer J, Scutella M, Pullalarevu R, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. *Intensive Care Med*. 2015;41:49-57.
133. Rachmale S, Li G, Wilson G, et al. Practice of excessive F(10(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respir Care*. 2012;57:1887-93.
134. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care*. 2011;15:R90.
135. Nelskylä A, Parr MJ, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest—an observational single centre study. *Scand J Trauma Resusc Emerg Med*. 2013;21:35.
136. Ihle JF, Bernard S, Bailey MJ, et al. Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest. *Crit Care Resusc*. 2013;15:186-90.
137. Empey PE, de Mendizabal NV, Bell MJ, et al. Therapeutic hypothermia decreases phenytoin elimination in children with traumatic brain injury. *Crit Care Med*. 2013;41:2379-87.
138. Hostler D, Zhou J, Tortorici MA, et al. Mild hypothermia alters midazolam pharmacokinetics in normal healthy volunteers. *Drug Metab Dispos*. 2010;38:781-8.
139. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: patients not treated with therapeutic hypothermia. *Resuscitation*. 2013;84:1310-23.
140. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. *Resuscitation*. 2013;84:1324-38.

Prognostication in Postcardiac Arrest Status

Kapil Zirpe, Sushma Patil

INTRODUCTION

Cardiac arrest is a major devastating event.^{1,2} Intensivists have to make decisions regarding appropriateness of admission to intensive care unit (ICU) and of providing treatment for post-cardiac arrest patients. Clinicians involved in the care of these patients are confronted with optimistic expectations of family. A multidisciplinary team has to provide predictions of long-term outcome. Postresuscitation care algorithm is well-established part of advanced life support "chain of survival".³ Neurological prognostication is now undertaken using a multimodal strategy and there is emphasis on allowing sufficient time for neurological recovery.²⁻⁴

EPIDEMIOLOGY

The yearly incidence of cardiac arrest is of about 50–110 per 100,000 people worldwide.⁴ Despite improvements in resuscitation techniques, mortality for those who suffer an out-of-hospital cardiac arrest (OHCA) is >90%.^{1,2} Among patients who achieve return of spontaneous circulation (ROSC), 40% survive to critical care admission and nearly 30% are discharged alive from hospital.² Survivors are left with severe neurological impairment. The most common cause of death depends on whether the cardiac arrest has occurred, in- or out-of-hospital. In OHCA, neurological injury accounts for two-thirds of all deaths, compared with only one-third in in-hospital cardiac arrest (IHCA).^{1,3} Time taken for ROSC determines overall outcome.

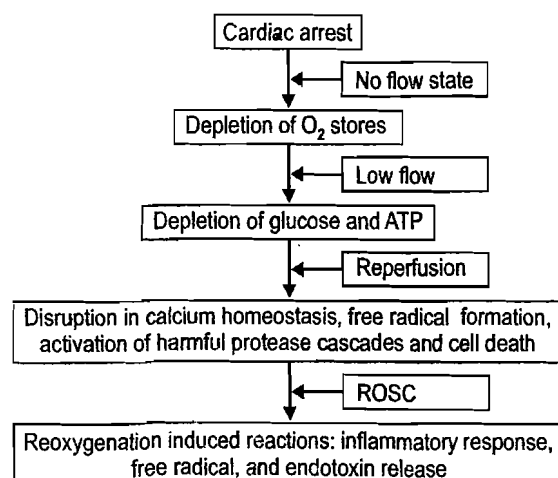
Factors Influencing the Neurological Time Taken for ROSC Determines Overall Outcome

- Out-of-hospital cardiac arrest or in-hospital cardiac arrest
- Response time, rates of bystander cardiopulmonary resuscitation (CPR), time to defibrillation, duration of CPR, quality of chest compression
- Cause of cardiac arrest (underlying pathological or trigger factor for cardiac arrest)

- Severity of postcardiac arrest syndrome (PCAS)
- Quality of treatment received during postresuscitation period, i.e., optimum support of cerebral and organ perfusion, and prevention of extracerebral systemic insults (e.g., hyperglycemia and infections)
- Rhythm before arrest (ventricular fibrillation or tachycardia)
- Access to emergent coronary angiography
- Implementation of targeted temperature management (TTM; induced mild hypothermia to 32°C or strict normothermia at 36°C for 24 h)
- Age.¹⁻⁴

PATHOPHYSIOLOGY

Cardiac arrest causes primary and secondary injury. The primary injury occurs at the time of arrest and is nonreversible. The secondary injury follows ROSC and subsequent cerebral reperfusion and is potentially reversible. Neuronal oxygen stores exhaust within 20 seconds leading to unconsciousness and within 5 minutes glucose and adenosine triphosphate (ATP) stores are depleted (Flowchart 1). Depletion of ATP leads



ATP, adenosine triphosphate; ROSC, return of spontaneous circulation.

FLOWCHART 1: Pathophysiology of postcardiac arrest events

to disruption in calcium homeostasis, free radical formation, and the activation of harmful proteases cascades and cell death. After ROSC, cerebral blood flow is also restored. Adenosine triphosphate is regenerated. This causes free radical formation and secondary cerebral injury. Cell death continues by apoptosis and necrosis. Cerebral autoregulation is impaired and cerebral edema develops secondary to hyperemic blood flow and inflammatory processes. Therapeutic hypothermia has role in limiting these mechanisms and thus, improve neurological outcome.^{1,5}

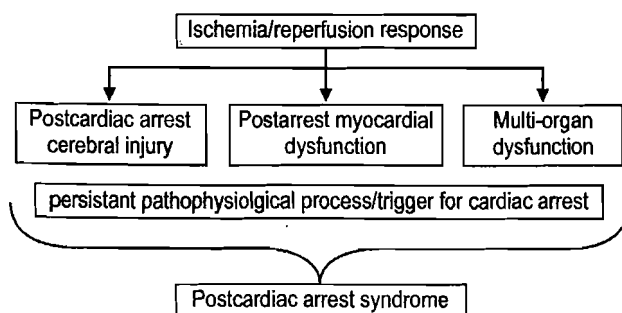
POSTCARDIAC ARREST SYNDROME

The combination of postcardiac arrest cerebral injury and ischemia or perfusion response coupled with postcardiac arrest myocardial dysfunction and multiorgan dysfunction and the persistent precipitating pathology defines the PCAS¹⁻³ (Flowchart 2). This syndrome was first defined by Vladimir Negovsky in 1972, a Russian pathophysiologist.^{1,6} It may not occur at all if the cardiac arrest is brief. Postcardiac arrest brain injury may manifest as coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction, and brain death. Cardiovascular failure accounts for most death within the first 3 days. Post-cardiac arrest syndrome activates immune and coagulation pathways leading to multiple organ failure and increasing risk of infection. Thus, sepsis and PCAS has common features (abnormality of microcirculation, vasodilation, intravascular volume depletion, hypotension, endothelial injury, and impaired autoregulation leading to hypoxemia, hypercarbia, pyrexia, hypo- or hyperglycemia, myocardial dysfunction).^{1,3,5}

Phases of Postcardiac Arrest Syndrome (Fig. 1)

Postcardiac arrest syndrome has five phases as per International Liaison Committee on Resuscitation documents.^{6,7}

1. Immediate care: Consists of initial 20 minutes following the return of spontaneous recovery of circulation.
2. Early phase: Twenty minutes to 6–12 hours, aggressive therapeutic measures are required for a successful outcome.



FLOWCHART 2: Components of postcardiac arrest syndrome

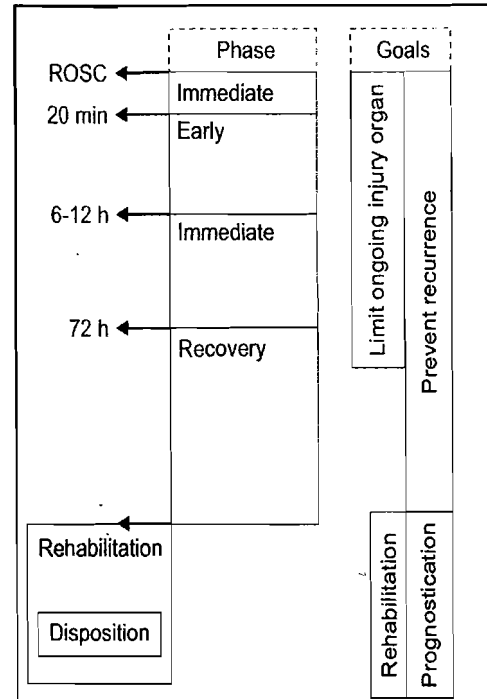


FIG. 1: Phases of postcardiac arrest syndrome

3. Intermediate phase: From 6–12 hours to 72 hours; surveillance and critical care treatment are required consistent with therapeutic objectives.
4. Recovery phase: After 72 hours by this time there is clearer diagnosis and more predictable results.
5. Rehabilitation phase: Focuses on the patient's complete recovery.

Postcardiac Arrest Treatment

The phases of PCAS should be treated with "goal-directed therapy". American heart association has recommended a post-cardiac arrest care bundle⁸⁻¹⁰ (Box 1).

Box 1: Postcardiac arrest care resuscitation care

Postcardiac arrest care bundle:

- Optimize ventilation and oxygenation: Target $\text{SaO}_2 \geq 94-6\%$, normocarbida
- Treat hypotension (SBP <90 mmHg): Target MAP 80–100
- Emergency coronary angiography: Patients with ST elevation and without ST elevation but suspected cardiovascular lesion
- Initiate targeted temperature management: target temperature between 32 and 36°C
- Prognostication: 72 h after ROSC (no TTM), 72 h after completion of TTM
- All patients who progress to brain or circulatory death after initial cardiac arrest should be considered potential organ donors

SBP, systolic blood pressure; MAP, mean arterial pressure; TTM, targeted temperature management; ROSC, return of spontaneous circulation.

Optimize Ventilation and Oxygenation

Control of Oxygenation

Postcardiac arrest patients; responding immediately to treatment, should be given oxygen via a facemask to maintain peripheral oxygen saturation of 94% or partial pressure arterial oxygen (PaO_2) >60 mmHg. Hypoxemia and hypercarbia both increase the likelihood of a further cardiac arrest and contribute to secondary brain injury. Evidences show that even hyperoxemia is harmful.² Hence, the inspired oxygen should be titrated to maintain the arterial blood oxygen saturation in the range of 94–98%.

Control of Ventilation

Consider intubation and ventilation in patient with obtunded cerebral function. End-tidal carbon dioxide (EtCO_2) and arterial blood gas are monitored to maintain normocarbica. Hypocarbica causes cerebral vasoconstriction and a decreased cerebral and coronary blood flow causing cerebral and coronary ischemia. Targeted temperature management decreases the metabolism and may increase the risk of hypocarbica. A sedation protocol is recommended. Bolus doses of a neuromuscular blocking drug may be required, particularly if using TTM. Short-acting sedation and neuromuscular drug are preferred is recommended. To detect seizures continuous electroencephalography (EEG) can be done in these patients, especially when neuromuscular blockade is used. A chest radiograph is advised to check the position of the tracheal tube, gastric tube and central venous lines, assess for pulmonary edema, and detect complications from CPR such as a pneumothorax associated with rib fracture.

Hemodynamic Management

Blood pressure should be maintained at systolic blood pressure <90 mmHg and mean arterial pressure (MAP) <65 mmHg.⁸

Hemodynamic instability is caused secondary to myocardial dysfunction. Early echocardiography should be performed in all patients to screen and quantify the degree of myocardial dysfunction. There is usually a transient requirement of inotropes. The systematic inflammatory response that occurs frequently in postcardiac arrest patients cause vasoplegia and vasodilation. This is treated with noradrenaline, with or without dobutamine, and fluid. Blood pressure (MAP), heart-rate, urine output, rate of plasma lactate clearance, central venous oxygen saturation, and serial echocardiography (ejection fraction, inferior vena cava diameter collapsibility) are monitored to guide treatment. Loss of cerebral autoregulation makes cerebral perfusion pressure dependent on MAP. Mean arterial pressure between 80 and 100 mmHg should be targeted. This is the range in which perfusion matches the cerebral metabolic activity.⁶

clearance.³ Tachycardia was associated with bad outcome in one retrospective study.³ In mild induced hypothermia, the normal physiological response is bradycardia. As long as blood pressure, lactate, mixed venous oxygen saturation (SvO_2), and urine output are adequate, bradycardia of 40/min may be left untreated.³ Relative adrenal insufficiency occurs frequently after ROSC. Postresuscitation shock should not be treated with steroids. Hyperkalemia is seen in immediate phase of PCAS. Subsequent, endogenous catecholamine release and correction of metabolic and respiratory acidosis causes intracellular transportation of potassium, causing hypokalemia. So, potassium level should be monitored and kept between 4.0 and 4.5 mEq/L.

Coronary Reperfusion

Acute coronary syndrome is an important cause of OHCA. In OHCA patients, cardiac catheterization should be performed immediately in the presence of ST-elevation and considered as soon as possible (<2 h) in other patients in the absence of an obvious noncoronary cause, particularly if they are hemodynamically unstable.^{3,5,6,8,9}

Targeted Temperature Control

Hyperthermia is common in the first 48 hours after cardiac arrest and a period of rebound hyperthermia after mild induced hypothermia is associated with increased mortality and worse neurological outcome.³ When the patient recovers spontaneous circulation, hypothermia reduces the metabolic consumption of oxygen and glucose.⁶

During the second phase, hypothermia reduces the formation of excitatory amino acids, particularly glutamate; thus prevents activation of the cytotoxic cascade, the formation of reactive oxygen species (ROS) and nitric oxide.⁶

During the third phase, hypothermia preserves the integrity of cell membranes and thus preventing the occurrence of cerebral edema, neuronal death and blood brain barrier injury.⁶

The advantages of therapeutic hypothermia have been very well-explained in a recent meta-analysis. Patients treated with therapeutic hypothermia exhibited improved neurological function [respiratory rate (RR) 1.55; 95 confidence intervals (CI) 1.22–1.96] and had a higher probability of survival at discharge (RR 1.35; 95 CI 1.10–1.65) compared to patients not treated with hypothermia.¹¹

Thus, all comatose (lacking meaningful response to verbal commands) adults should have TTM with target temperature between 32°C and 36°C and then maintained for at least 24 hours.^{3,8,9} Cooling should be started immediately after ROSC.³ There are various methods of inducing and/or maintaining TTM.³

Other factors to be considered important for optimizing neurological recovery are seizures and blood glucose control. Myoclonus can be difficult to treat.

Blood glucose should be maintained at 180 mg/dL and hypoglycemia should be avoided hypothermia is associated with higher blood glucose values, increased blood glucose variability, and greater insulin requirements.

Prognostication

Prognostication of postcardiac arrest patient is challenging. Hypoxic-ischemic brain injury is common after resuscitation from cardiac arrest. Two-thirds of those dying after admission to ICU following OHCA die from neurological injury due to the cost burden and prognostication of a poor neurological outcome. Most of these deaths are due to active withdrawal of life-sustaining treatment (WLST). Ideally, the false-positive rate (FPR) of tests used for predicting poor outcome, should be zero with narrowest possible CI. However, most of studies involving prognostication had few patients, even if the FPR is 0%, the upper limit of the 95% CI is often high. And many of these studies are confounded by self-fulfilling prophecy, which is a bias occurring when the treating physicians are not blinded to the results of the outcome predictor and use it to make a decision on WLST. Targeted temperature management and sedatives or neuromuscular blocking drugs may potentially interfere with prognostication indices, especially those based on clinical examination.^{3,4}

PREDICTING PATIENTS SURVIVAL IMMEDIATELY AFTER RETURN OF SPONTANEOUS CIRCULATION AFTER CARDIAC ARREST

Immediate prediction in a postcardiac arrest patient is done from immediately available clinical and physiological information.

- Patient characteristics: Age⁵
- Speed and quality of prehospital care: As mentioned earlier shorter time to CPR, shorter duration of CPR, initial rhythm of ventricular fibrillation or ventricular tachycardia have been associated with improved outcome^{1,3,5}
- Cause of cardiac arrest: Asphyxia, and to a lesser degree, all extra cardiac causes, are predictors of poor prognosis.⁵ In contrast, sudden nonrespiratory cardiac death is usually associated with better prognosis.

None of these characteristics can give assurance for survival or nonsurvival. Thus, prognostication cannot be done on the circumstances of cardiopulmonary resuscitation. Few scoring system have been developed to predict survival immediately after cardiac arrest.

These include the prognosis after resuscitation (PAR) score (Table 1) and OHCA score.¹ The OHCA score is cumbersome and cannot be used in the ward or in emergency, since it is difficult to estimate accurately "no-flow" and "low-flow" times. The PAR score was based on retrospective

TABLE 1 Prognosis After Resuscitation score

Variable	Score
Metastatic malignancy	10
Nonmetastatic malignancy	3
Sepsis	5
Dependent functional status	5
Pneumonia	3
Creatinine >1.5 mg	3
Age >70 years	2
Acute myocardial infarction	-2

Note: Prognosis After Resuscitation score >5 indicates nonsurvival.

analysis of IHCA.¹² The PAR score is more straightforward and score >5 predicts nonsurvival. However, clinicians are not recommended to use the PAR score as a sole reason to determine admission to critical care.

PREDICTING NEUROLOGICAL OUTCOME AFTER CRITICAL CARE ADMISSION

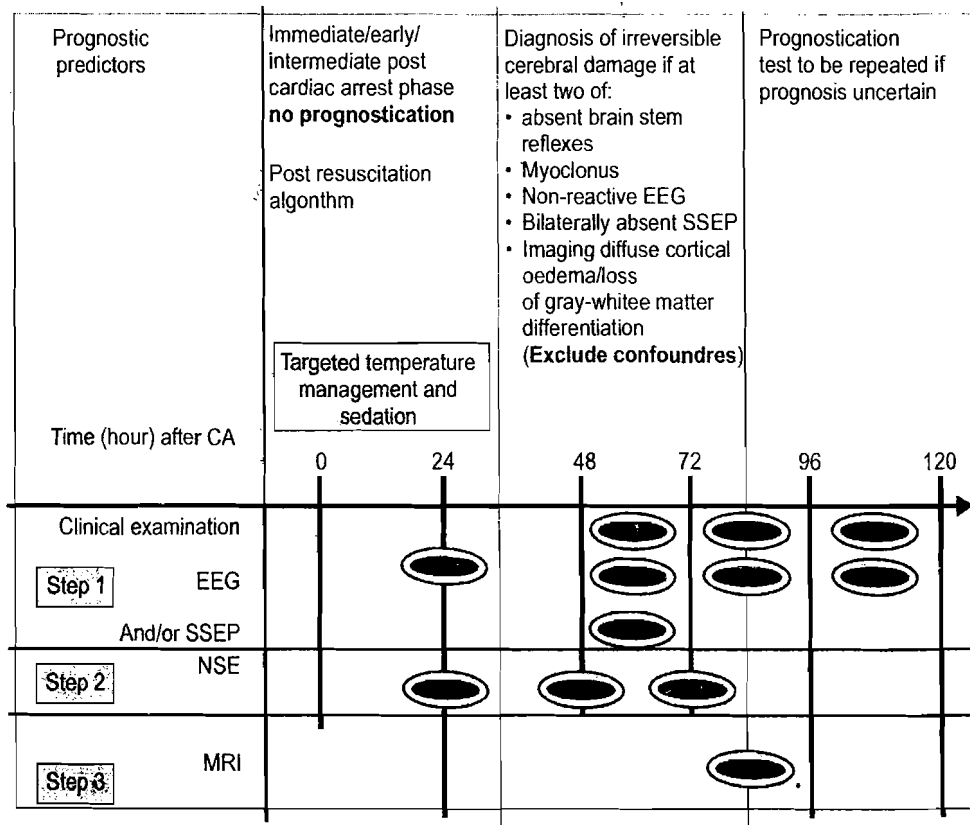
Neurological function after cardiac arrest is usually assessed using cerebral performance categories^{1,4} (Table 2) and Glasgow Outcome Scoring system. These score are unhelpful in immediate coarse after ROSC.⁴ A stepwise multimodal strategy, paying specific attention to appropriate timings and combination of prognosticators should be adopted (Flowchart 3).

Clinical Examination

Neurological examination is gold standard in prognostication because it directly evaluates brain function. After reperfusion, brainstem functions-spontaneous breathing and reflexes return rapidly followed by reflexes related to deep structures. Assessment of brainstem reflexes, motor responses to pain, and myoclonus during the first 72 hours after arrest represented poor prognosis.² Target temperature management (target temperatures of 32–36°C) and residual sedation can alter this clinical finding making repeated assessment necessary. The predictive value of clinical examination might be limited by some degree of confirmatory bias. While predictors of poor outcome based

TABLE 2 Cerebral performance categories

Cerebral performance categories	Outcome class
Back to baseline good cerebral performance	Good
Moderate impairment	Good
Severe impairment	Poor
Comatose or vegetative	Poor
Dead	Poor



EEG, electroencephalogram.

FLOWCHART 3: Multimodal strategy for prognostication

on clinical examination are inexpensive and easy to use. The treating team cannot be concealed from tests used for clinical examination and therefore their interpretation may influence clinical management and cause a self-fulfilling prophecy.³

Pupillary and Corneal Reflexes

Fixed dilated pupils or bilateral absence of pupillary light reflexes at 72 hours after cardiac arrest is a robust indicator of poor prognosis, whether the patient undergoes TTM or not [FPR 0.5% (95% CI 0–2) vs. 0.5% (0–8)].^{3,4} Although absence of pupillary reflexes during the first 24 hour after arrest does not suggest good outcome, particularly in hypothermic patients [8% (1–25)], presence of pupillary reflexes at 72 hours does not indicate good prognosis [predictive value 61% (95% CI 50–71)]. Absence of corneal reflexes at 72 hour indicates poor prognosis [FPR 5% (0–25)], but with lower certainty than pupillary reflexes, especially in patients who have received sedatives or neuromuscular blockade. The presence of corneal reflexes is an unreliable predictor of good outcome [predictive value 62% (95% CI 51–72)].^{2,4,13}

Motor Response

- 34** Absent or extensor response to pain 72 hours after cardiac arrest is reliable predictor of poor outcome.^{2–4,13} This test can

be confounded by sedatives, opiates, and neuromuscular blockade; and TTM [FPRs up to 24% (95% CI 6–48)]. For assessment of motor responses, a strong stimulus should be applied to the patient and the residual effects of sedative drugs need to be excluded. The residual effect of sedatives can be prolonged in TTM or due to reduced metabolic clearance (e.g., renal or liver dysfunction), or both.^{2,3} The elicited response is influenced by timing at which it is done and therefore its prognostic accuracy. However, one should remember that an extensor or absent response does not necessarily signify a poor prognosis. On the other hand flexor or even a localized movement does not indicate that the patient will recover [positive predictive value 81% (95% CI 66–91)].⁴ In TTM treated patient, absence of motor response even after fourth day of arrest, cannot be used as a single predictor of poor outcome.

Myoclonic status has been known to predict poor outcome after cardiac arrest, but there have been reports of patients who have recovered well despite having early postanoxic myoclonus.^{1,2} Prognostic certainty has been questioned.² Up to 9% of patients with myoclonus survive.^{2,3} The precise definition of myoclonus should be clarified as not all twitches are myoclonus. Generalized status myoclonus (multifocal spontaneous twitches) lasting for duration of 30 minutes, occurring even under TTM and sedation, is commonly associated with malignant, unreactive EEG patterns suggests with poor outcome [FPR 0% (95%

CI 0–3)].^{2–4} Brief myoclonic jerks restricted to the face or trunk, controllable with sedatives, and accompanied with a more benign (i.e., continuous and reactive) EEG, do not suggest poor outcome [up to 11% (3–26)]. Interpretation clinical assessment and myoclonus should be carefully done on the background of other predictors, especially EEG.

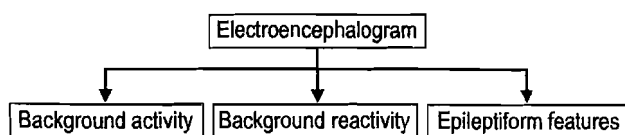
Thus, on the third day absent pupillary or corneal reflexes and absent or extensor motor response predicts a poor neurological outcome in postcardiac arrest status patient.¹³

Electroencephalography

Electroencephalographs are signals generated by cortical postsynaptic potentials. It is widely available, noninvasive, inexpensive, and provides real-time investigation of electrical brain activity. The use of EEG is used to detect seizures and postanoxic status epilepticus, which is seen in 10–40% of patients and are associated with poor outcome.^{2–4} For decades, it has been routinely used in coma prognostication. Electroencephalograph is very informative because several EEG features correlate with degree of neuronal injury. The availability of computed tomography (CT) and magnetic resonance imaging (MRI) compatible electrodes has facilitated the use of continuous EEG in the intensive care setting. The development of automated EEG screening has made EEG interpretation easy. Electroencephalogram recording should be started 12-hour after cardiac arrest.⁴ The American Clinical Neurophysiology Society has published standardized guidelines for EEG interpretation, which have been validated in the setting of coma prognostication. Electroencephalogram findings can be classified into three main aspects, discussed in the following three sections (Flowchart 4).

Background Activity

Electroencephalography activity are not affected by mild hypothermia, whereas sedative drugs used during TTM can interfere in EEG measurement (especially background and reactivity), depending on the drug and dose used. However, several studies reveal that sedative infusions of midazolam in the range of 0.1–0.2 mg/kg/h or of propofol in the range of 2–3 mg/kg/h, prognostic accuracy of EEG is maintained in first 24 hours, with or without TTM. After 2–3 days in patient's receiving sedation, the accuracy of EEG measurement is reduced. If the patient receives sedative doses higher than those mentioned above, EEG findings should be interpreted with caution. Background activity represents global cerebral



FLOWCHART 4: Use of electroencephalogram for prognostication

Box 2: Background electroencephalogram activity with poor and good outcome

Poor outcome	Good outcome
<ul style="list-style-type: none"> • Appearance of low-voltage (<20 μV) or isoelectric (suppressed) background at 24 h [FPR 0% (95% CI 0–17)] • Burst suppression at any time [0% (0–11)] • Burst suppression with identical bursts [0% (0–17)] • Spontaneously discontinuous background during TTM [7% (0–24)] 	<ul style="list-style-type: none"> • Continuous background activity as early as 12 h after cardiac (positive predictive value 92%) • Normal voltage background at 24 h [positive predictive value 72% (53–86)]

FPR, false positive rate; CI, confidence interval; TTM, targeted temperature management.

functioning. Anoxic-ischemic injury causes neuronal damage causing decreased amplitude and slowing of background activity. Electroencephalogram findings associated with poor prognosis and good outcome^{2–4,13,14} (Box 2). An exception to good prognosis related to background activity is an EEG indicative of alpha coma. This is associated with poor prognosis of patients.

Background Reactivity

Here auditory or noxious stimuli is given, EEG response recorded is called as reactivity and is recorded as either as a transient attenuation or increase in electrical activity. If assessed after TTM [FPR 7% (CI 1–15)], absence of reactivity indicates poor prognosis, prognostication becomes stronger if done during TTM [2% (0–9)]. In about 15% of patients rhythmic, periodic, or ictal discharges are seen after stimulus, these are not physiological reactivity, and herald poor prognosis [FPR 2% (0–11)], particularly if recorded during TTM or sedation. Presence of reactivity if recorded during TTM indicates good prognosis [positive predictive value 86% (77–92)].^{4,14}

Limitation of Electroencephalography

Error can occur because of

1. Lack of a standard definitions and classifications for different EEG patterns.
2. The diagnosis of absent or present EEG reactivity relies on the experience and expertise of the neurologist who interprets the EEG.
3. The exact degree of stimulus needed to reproduce EEG changes and reactivity has not been standardized. Standardization of stimulus protocol can overcome this drawback. Muscle activity occurring after weaning from sedation may produce artifacts and necessitate muscle relaxation.^{2,3}

Epileptiform Features

Occurrence of sharp waves, spikes, poly-spikes, and waves, collectively described as epileptiform features. If these features occur after TTM, it is associated with poor outcome [FPR 9% (CI 2-21)]. In some patients with preserved brainstem reflexes EEG suggesting status epilepticus appears after TTM and sedation weaning, and have, background reactivity, and somatosensory evoked potentials, these patients can be predicted to have reasonable functional recovery. Patients with abovementioned features suggesting a potentially good prognosis should be treated aggressively with anticonvulsants. Suggested optimum duration for treatment in such patient is not known, but extension beyond 2 weeks is not recommended.^{3,4,13}

Standard or Continuous Electroencephalography

Two standard EEG recordings of 20-30 minutes with background reactivity recording done within 48 hours of cardiac arrest are said to be as informative as continuous EEG. The only recommendation of continuous EEG is monitoring of postanoxic status epilepticus. Repeated assessments may be needed as electrical activity can change with time, particularly, during the first 72 hours after cardiac arrest; in such case continuous EEG is preferable.^{2,4,13}

Bispectral Index

A bispectral index (BIS) consists of a special designed electrode which is attached to patient's head and a BIS value between 0 and 100 is obtained indicating cerebral activity. In TTM, a BIS value ≤ 22 and a burst suppression ratio of ≥ 48 immediately after first dose of neuromuscular block are associated with poor neurological prognosis.¹ However, prediction may be wrong in up to 10% of patients. In combination with clinical and other indicators of poor neurological prognosis, BIS may provide additive information.¹

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEP) is noninvasive method that involves monitoring of brain response to electrical stimulation to one of the peripheral nerves. For this test, peripheral nerve should be intact. In cardiac arrest patients, median nerve is most commonly stimulated bilaterally at wrist. Electrodes are placed at elbow-Erb's point on the cervical medulla and on the parietal and frontal cortex. Specific responses are identified as N9 for Erb's point, N14 for cervical medulla, and N20 for cortex.

The two types of SSEP studied are early latency evoked potentials and middle latency evoked potentials. Early latency evoked potentials are being studied in setting of post-cardiac arrest status.

Early-latency Evoked Potentials

Early latency evoked potentials is done by the averaging of cortical electrographic responses of afferent pathway generated after repetitive stimulation of nerve. A repetitive electrical stimulations is applied to the median nerve, it is transmitted to the contralateral postcentral gyrus, and recorded about 20 minutes after the stimulation (N20). It is represented by a negative deflection. Bilateral absence of the N20 response is strongly indicates poor outcome, both during [FPR 0% (95% CI 0-2)] and after [0.5% (0-2)] TTM.^{1-4,13} The accuracy of evoked potentials is extremely high for prediction of poor prognosis. The accuracy in predicting a favorable outcome of bilaterally present N20 range from 40% (29-50) to 58% (49-68). This is extremely low compared to continuous reactive EEG (approximately 80%). Evoked potentials have a lower sensitivity than the absence of reactivity on EEG to predict a poor outcome [43% (31-57) and 74% (62-84), respectively]. Thus, early latency evoked potentials do not provide additional information compared to EEG, clinical assessment, and biomarkers. Quantitative assessment of N20 amplitude has been suggested to offer additional prognostic information.²⁻⁴

Middle-latency Evoked Potentials

Middle-latency evoked potentials are intracortical associative interactions and can be recorded up to 100 minutes after stimulation. They are recorded by averaging the response to several stimuli to cancel out the background EEG noise. Middle-latency evoked potentials shows better functional connectivity than early-latency evoked potentials; but are difficult to record. The presence of middle-latency responses has been reported to have a positive predictive value for awakening as high as 97%, to as low as only 28%. The presence of pain induced middle-latency evoked potentials strongly predicts recovery of consciousness (positive predictive value of 100%).⁴

Limitation of Somatosensory Evoked Potentials

It has only moderate interpretation reproducibility. Electrical ICU equipment that can interfere with readings should also be turned-off whenever possible. Providing more stimuli (up to 1,000 or more) and increasing the stimulus intensity can also improve accuracy.²

Biochemical Markers

Cardiac arrest status causes cerebral hypoxia leading to destruction neurons and astrocytes. Thus, wide range of proteins is released in blood and can be used as markers for cellular injury. These biomarkers are quantifiable biological substances, measured in peripheral blood. Only two markers

are extensively studied neuron specific enolase (NSE marker of neuronal damage) and S-100 β (marker of astrocyte damage).

Neurospecific Enolase

Neurospecific enolase is an isomer of enolase, a cytoplasmic glycolytic neuronal enzyme present in neurons and neuroendocrine cells. Before advent of TTM serum, NSE concentration of >33 $\mu\text{g/L}$ between 24 and 72 hours after cardiac arrest is strongly suggest poor outcome [FPR 0% (95% CI 0-3)].²⁻⁴ However, studies after advent of TTM showed variable results, maximal concentration in patient with good outcome ranging from 48 $\mu\text{g/L}$ at 24 hours to 80 $\mu\text{g/L}$ at 72 hours. The reliability in patient who receives TTM at 33°C is questionable. Present data suggest that patients with a serum NSE concentration in excess of 80 $\mu\text{g/L}$ within the first 72 hours after cardiac arrest have poor prognosis. Serum concentrations of <33 $\mu\text{g/L}$ are related to good outcome [positive predictive value 63% (52-73)]; thus, it is suggested not to apply a single threshold for prediction of good or poor outcome. The trend of serum NSE concentration measurements taken over the first 72 hours could be more accurate in predicting outcome than a single value.

Limitations

An important caveat to the use of biomarkers is sample collection, heterogeneous measurement techniques, and the skills of the laboratory staff. Biomarker concentrations could also theoretically increase because of hemolysis in patients who are treated with extracorporeal membrane oxygenation. Neurospecific enolase is present in neuroectodermal cells and high concentrations can be seen in patients with small-cell lung carcinoma.^{2-4,13}

Serum S-100 β Protein

Serum S-100 β protein is released by glial cells after brain insult. Extracerebral sources are adipose tissue and muscle. It has got short half-life so S-100 β concentration increases quickly after hypoxia induced injury. Even within 24 hours of cardiac arrest, high concentrations >0.5 $\mu\text{g/L}$ indicates poor prognosis.^{2,4,13} Plasma level of S-100 depends on renal function.¹⁴

Due to less availability of test and variable threshold for poor outcome, this biomarker is less commonly used.

Neuroimaging

Brain imaging reveals structural alterations and quantifies the postcardiac brain injury.

Imaging studies have advantage that is unaffected by sedative drugs.¹³

Computed Tomography Brain

Computed tomography provides valuable information if the cause of cardiac arrest is uncertain and helps to rule out intracerebral bleed. Computed tomography indications of brain hypoxia include loss of or reduced gray or white matter discrimination and sulcal edema or effacement.^{2-4,13,14} They appear more prominent in central areas such as basal ganglia and thalami.¹⁴ Loss of GM or WM discrimination within 2 hours of cardiac arrest seems a reliable predictor of poor outcome [FPR 0% (95% CI 0-12)]^{3,4} but has is poor [positive predictive value 37% (9-75)] for predicting good prognosis. The sensitivity was extremely low (3.5-6%).

Magnetic Resonance Imaging Brain

Magnetic resonance imaging has higher resolution than CT, identification of structural abnormalities in the neocortex, deep grey nuclei, and hippocampi is easier. The use of MRI (particularly diffusion-weighted MRI) is preferred. In patients with a poor outcome, occipital and mid-temporal cortex and the putamen can show restricted diffusion, suggestive of cytotoxic edema.^{2,4,14} Analysis of diffusion-weighted MRI across different brain areas have shown an FPR of 0% (95% CI 0-22) for predicting poor outcome, with excellent inter-rater agreement. Furthermore, absence of diffusion changes does not consistently predict a good outcome [positive predictive values 73% (45-92)80 or 75% (63-85)]. It is recommended that MRI be done between 24-48 hours and 7 days after cardiac arrest.

Limitations

The risk during transportation to the scanner of patients who are critically ill and the unclear prognostic value of imaging techniques (especially when assessed only qualitatively), explain why imaging remains optional in most prognostication algorithms.

In practice, brain CT is recommended if cause of cardiac arrest is unknown. Brain MRI can be considered in centers where appropriate resources and expertise are present, to complement multimodal assessments. It is also preferred in patients who are in persistent coma for several days, where prognostic signs of poor outcome with clinical, electrophysiological, and blood tests are uncertain.

SUGGESTED PROGNOSTICATION STRATEGY

Multimodal assessment is supported by a growing body of evidence and is strongly advocated whenever doubt persists because each single method when used alone carries risks of false prediction.^{2-4,14,15} Apart from increasing safety, limited

evidence also suggests that multimodal prognostication increases sensitivity. It is applicable to all patients who remain comatose with an absent or extensor motor response to pain at 72 hours from ROSC.

Timing of Neurological Prognostication

In previous guidelines, 72 hours after cardiac arrest has been established as a suitable time for prognostication because by this time, several clinical findings can support an unfavorable prognosis with a very high certainty, and patients with a favorable prognosis have typically regained consciousness.¹⁴ Electroencephalogram can be done 12–24 hours after cardiac arrest.³ In multimodal algorithm, clinical examination and electrophysiological studies (EEG, evoked potentials, or both) should be carried out after return to normothermia and sufficient time after discontinuation of sedation. At earliest prognostication should be done at 48 hours postcardiac arrest. Repeat examination is mandatory at 72 hours in those who do not show clear signs of awakening. Since induced hypothermia changes the conditions for the clinical neurological examination, postpone the final assessment in hypothermia treated patients to at least 72 hours after normothermia, i.e., approximately 4.5 days after the arrest.

Stepwise Prognostication

Rule out Confounders

Major confounders like sedation and neuromuscular blockade, hypothermia, severe hypotension, hypoglycemia, and metabolic and respiratory derangements need to be excluded. Suspend sedatives and neuromuscular blocking drugs for long enough to avoid interference with clinical examination. When residual sedation or paralysis is suspected, antidotes to reverse the effects of these drugs should be considered.

Step 1: An attempt is made to search an optimum combination of prognostic variables, clinical assessment (particularly myoclonus and brainstem reflexes), EEG background reactivity, and serum NSE concentrations seem to have the best predictive value to identify patients with a poor outcome. So far, no combination of tests heralding good prognosis have sufficient high quality evidence. A careful clinical neurological examination remains the foundation for prognostication of the comatose patient after cardiac arrest perform a thorough clinical examination daily to detect signs of neurological recovery or to identify a clinical picture suggesting that brain death has occurred. Result of prognostic tests which were carried need to be also considered at this time point. Evaluate the most robust predictors first. These predictors have the highest specificity and precision (FPR 5% with 95% CI 5%) in patients treated

with controlled temperature.^{3,4} They include bilaterally absent pupillary reflexes at 72 hours from ROSC and bilaterally absent SSEP N20 wave after rewarming (this last sign can be evaluated at 24 hours from ROSC in patients who have not been treated with controlled temperature). Based on expert opinion, we suggest combining the absence of pupillary reflexes with corneal reflexes for predicting poor outcome at this time. Ocular reflexes and SSEPs maintain their predictive value irrespective of target temperature.

Step 2: Diagnosis of irreversible cerebral damage if at least two of these predictors are present:

1. Absent brainstem reflexes.
2. Early status myoclonus (within 48 hours from ROSC).
3. An unreactive malignant EEG pattern (burst-suppression, status epilepticus) after rewarming.
4. The presence of a marked reduction of the GM/WM ratio or sulcal effacement on brain CT within 24 hours after ROSC or the presence of diffuse ischemic changes on brain MRI at 2–5 days after ROSC.

By this time concentration reports of biomarkers should be available. High values of serum NSE at 48–72 hours after ROSC are considered in poor outcome. Measuring trends in NSE levels is highly valuable prognostic marker as it reduces the risk of false-positive results.

Step 3: This involves only imaging technique (MRI). When prolonged sedation and/or paralysis is necessary, for example, because of the need to treat severe respiratory insufficiency, we recommend postponing prognostication until a reliable clinical examination can be performed. When dealing with an uncertain outcome, clinicians should consider prolonged observation.

ORGAN DONATION

Organ donation counseling should be considered in:

- Who fulfill criteria for brain death after ROSC is achieved
- Comatose patients in whom a decision is made to withdraw life-sustaining therapy
- After circulatory death occurs
- Individuals where CPR is not successful in achieving ROSC.

All decisions concerning organ donation must follow local legal and ethical requirements, as these vary in different settings.

NEW PROGNOSTIC METHODS

Some of the future prognosticators are automated pupillometry, long-latency evoked potentials, and other biomarkers such as plasma neurofilament heavy-chain protein, 96 serum glial fibrillary acidic protein, brain-derived neurotrophic factor, and tau protein and cerebral oxygenation.

CONCLUSION

Prognostication after cardiac arrest has become an integral part of post-resuscitation care.

It has progressed to a multimodal strategy which integration of clinical examination and judicious of information provided by many tests. Prognostication should never be based on a single indicator; although some variables have a very low FPR for poor outcome. Multimodality assessment increases the reliability of a prognostic estimation.^{2-4,14.}

REFERENCES

1. Temple A, Porter R. Predicting neurological outcome and survival after cardiac arrest. *Contin Educ in Anaesth Crit Care Pain*. 2012;12(6):283-7.
2. Taccone FS, Cronberg T, Friberg H, et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. *Crit Care*. 2014;18(1):202.
3. Nolan JP, Soar J, Cariou A, Cronberg T, et al. European resuscitation council and European Society of Intensive care medicine 2015 guidelines for post-resuscitation care. *Intensive care Med*. 2015;41:2039-56.
4. Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurology*. 2016;15(6):597-609.
5. Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome: from immediate resuscitation to long term outcome. *Ann Intensive Care*. 2011;1(1):45.
6. Vargas JRN, Diaz JL. Post cardiac arrest syndrome. *Colombian Journal of Anesth*. 2014;42(2):107-13.
7. Neumar RW, Nolan JP, Adrie C, et al. A consensus statement from International Liaison Committee on Resuscitation; the American heart association emergency cardiovascular care committee; Post cardiac arrest syndrome. *Circulation*. 2008;118(23):2452-83.
8. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 Suppl 2):S465-82.
9. Nolan JP, Deakin C, Lockey A, et al. International Liaison Committee on Resuscitation Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Science with treatment recommendations. *European resuscitation council*. 2015;95:e1-31.
10. Reynolds JC, Lawner BJ. Management of Post-cardiac arrest syndrome. *J Emerg Med*. 2012;42(4):440-9.
11. Arrich J, Holzer M, Harvel C, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev*. 2012;9:CD004128.
12. Ebell MH. Prearrest predictors survival following in-hospital cardiopulmonary resuscitation :a meta-analysis. *J Fam Pract*. 1992;34(5):551-8.
13. Samaniego EA, Persoon S, Wijman CA. Prognosis after cardiac arrest and Hypothermia: A new Paradigm. *Curr Neurol Neuroscience Rep*. 2011;11(1):111-9.
14. Cronberg T, Brizzi M, Liedholm LJ, et al. Neurological Prognostication after cardiac arrest—Recommendations from Swedish resuscitation Council. *Resuscitation*. 2013;84(7):867-72.
15. Blondin NA, Greer DM. Neurologic Prognosis in Cardiac Arrest Patients treated with Therapeutic Hypothermia. *Neurologist*. 2011;17(5):241-8.

Barriers and Controversies in Implementation of Induced Hypothermia

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INTRODUCTION

Sudden cardiac arrest constitutes to be a major public health burden across the world. Despite advances in protocolized cardiopulmonary resuscitation (CPR) and postresuscitation care, survival rates of those who present with either in- or out-of-hospital cardiac arrest (OOHCA) are still poor. In those successfully resuscitated from cardiac arrest, subsequent mortality is still high. For OOHCA, survival to hospital discharge was only 9.5% and for in-hospital cardiac arrest survival to discharge was only 23%.¹ Initial ischemic insult of cardiac arrest followed by subsequent reperfusion injury of resuscitation, termed ischemia-reperfusion injury is the prime reason for postarrest syndromes.^{2,3} Clinically, the most sinister result of ischemia following cardiac arrest is brain injury.⁴ In all reported series, the most common cause of death or withdrawal of life-sustaining therapy is brain injury.^{4,5} Consequently, various proposed strategies have been directed at ameliorating neurological injury following return of spontaneous circulation (ROSC). One of the most promising therapies in this respect has been induced hypothermia (IH), also referred to as therapeutic hypothermia (TH) or targeted temperature management (TTM).

HISTORICAL BACKGROUND

Hypothermia's role in attenuating injury has been recognized historically.⁶ Animal studies of 1950s and 1954 by Hegnauer and D'Amato demonstrated decreased oxygen consumption in hypothermic dogs.⁷ The first human study by Benson et al. in 1959 demonstrated decreased mortality with hypothermia after cardiac arrest.⁸

Two studies published in the February 2002 in New England Journal of Medicine demonstrated improved survival and neurological outcomes with induction of mild IH for comatose survivors of OOHCA (Table 1), thereby making implementation of IH a regular medical intervention in these kinds of patients.

Bernard et al. examined the endpoint of survival to hospital discharge to home or a rehabilitation facility (good outcome) in 77 patients, and demonstrated favorable neurological outcome in hypothermia group (49%) compared with normothermic group (26%).⁹

The Hypothermia After Cardiac Arrest (HACA) Study Group showed that, when applied to unconscious OOHCA patients with ROSC ($n = 274$), mild hypothermia (cooling to 32–34°C) provided significant improvement in functional recovery at hospital discharge [55% vs. 39%; number needed to treat (NNT) = 6] and lower 6-month mortality rate when compared with patients who were not cooled (41% vs. 55%) (NNT = 7).¹⁰

Subsequently, two large studies published in 2013 raised fresh questions regarding IH in post-cardiac arrest patients. The TTM study,¹¹ which evaluated IH to a target temperature of 33 versus 36°C, failed to find a difference in outcome (cerebral performance category scale, modified Rankin scale and mortality) between the two groups. They actively controlled the temperature during the intervention period and aimed to prevent fever during the first 3 days after cardiac arrest (Table 2). Kim et al.¹² studied the effect of prehospital induction of mild hypothermia, using infused cold saline by paramedics in the field, on survival and neurological status and found that this intervention did not improve either of these endpoints.

In a retrospective cohort study a correlation between the duration of the circulatory standstill, defined as no-flow time, and the effect of IH was studied. The authors concluded that the benefit of IH of 32–34°C increased with cumulative duration of circulatory standstill, being significant with a no-flow time of more than 2 minutes [odds ratio (OR) 2.72; 95% confidence interval (CI): 1.35–5.48] resulting in a maximum benefit beyond 8 minutes (OR 6.15; 95% CI: 2.23–16.99).¹³ In addition, a recent study¹⁴ revealed a significant effect of the overall duration of CPR efforts, defined as low-flow time, on survival and neurologic outcome of cardiac arrest victims. In this study, patients undergoing IH of 32–34°C

had increased odds of a favorable neurologic outcome with an overall resuscitation time below 29 minutes (OR 2.89; 95% CI: 1.53–5.43).¹⁵

TABLE 1 Comparison of Bernard study (2002) to Hypothermia After Cardiac Arrest (2002) study

	Bernard et al., 2002	Hypothermia After Cardiac Arrest, 2002
Design	Randomized clinical trial with blinded assessment of endpoint	Randomized clinical trial with blinded assessment of endpoint
Chief inclusion	<ul style="list-style-type: none"> Initial rhythm VF Successful ROSC Persistent coma after ROSC 	<ul style="list-style-type: none"> Witnessed cardiac arrest Initial rhythm VF or nonperfusing ventricular tachycardia Age 18–75 years Estimated 5–15 min from collapse to first attempt at resuscitation ≤60 min from collapse to ROSC
Chief exclusion	<ul style="list-style-type: none"> Age <18 years (men) Age <50 years (women) Cardiogenic shock Possible causes of coma other than cardiac arrest 	<ul style="list-style-type: none"> Tympanic membrane temperature <30°C on admission Pregnancy Response to verbal commands after ROSC and before randomization Cardiogenic shock Significant hypoxemia after ROSC
Total enrolment	77	275
Outcome: favorable neurology at discharge	49% (hypothermia) vs. 26% (normothermia) p = 0.046, APR 23%, NNT 4.3	55% (hypothermia) vs. 39% (normothermia) p = 0.02, ARR 14%, NNT 7

ROSC, return of spontaneous circulation; VF, ventricular fibrillation; ARR, absolute risk reduction; APR, annual percentage rate; NNT, number needed to treat

Considering the findings of above studies, various international organizations have strongly recommended IH after resuscitation and ROSC of CA. The International Liaison Committee on Resuscitation (ILCOR) has since stated, “Unconscious adult patients with spontaneous circulation after OOHCA should be cooled to 32–34°C for 12–24 hours when the initial rhythm was ventricular fibrillation and that such cooling may also be beneficial for other rhythms or in-hospital CA.”¹⁶

The European Resuscitation Council (ERC) reinforces this recommendation and states that IH is “safe and effective even if there is lack of experience.”¹⁷ This practice has been rather liberally applied in the academic tertiary care environment, in the community hospital setting and in the prehospital environment.^{18–20}

American Heart Association (AHA) joined the hypothermia recommendations through its algorithms for Advanced Cardiac Life Support 2015 guidelines in which it also recommended that IH can be deployed in the comatose (i.e., lack of meaningful response to verbal commands) adult patients with ROSC after cardiac arrest have TTM.²¹

PHYSIOLOGICAL CONSEQUENCES OF INDUCED HYPOTHERMIA AND ITS IMPLICATIONS

The key to understanding the various benefits, harms, barriers, and limitations of IH lies in understanding the pathophysiology of post-cardiac arrest syndromes and the hypothesized mechanisms of action of IH in ameliorating these pathophysiological processes (Fig. 1).

Cardiac arrest and ROSC is a case of whole body ischemia and subsequent reperfusion injury. This injury mechanism along with prearrest comorbidities causes enormous biochemical, structural, and functional insults, which is a complex inter-related processes leading to progressive cell destruction, multiorgan dysfunction, neuronal apoptosis, and programmed cell death.²²

Many studies have shown that hypothermia can interrupt these temperature sensitive early stages of apoptotic pathway, thereby contributing to protection of the brain and heart.

TABLE 2 Outcomes of targeted temperature management at 33°C versus 36°C after cardiac arrest¹¹

Outcomes	33°C group	36°C group no/total number (%)	Hazard ratio or risk ratio (95% confidence interval)	p value
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up				
Cerebral performance category of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.66)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

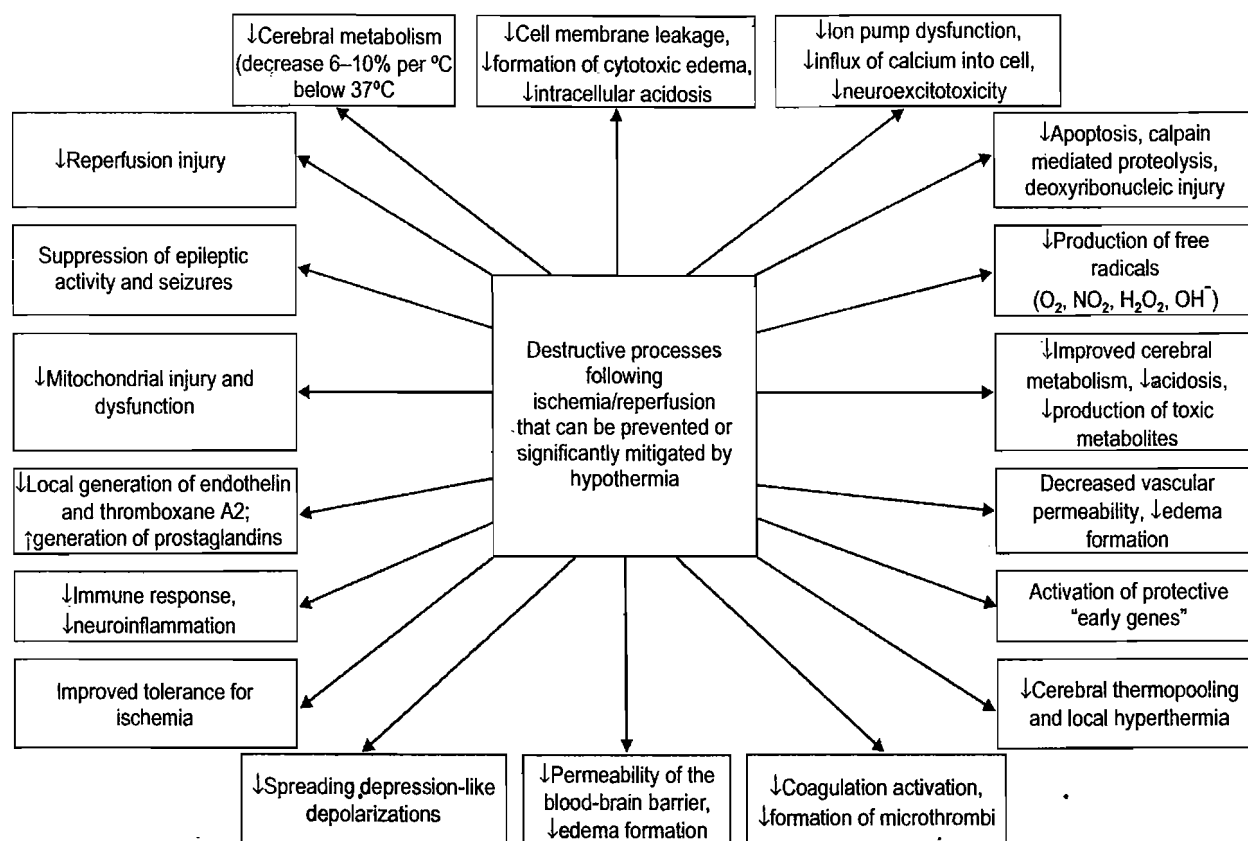


FIG. 1 Mechanisms underlying the protective effects of mild-to-moderate hypothermia

Under hypothermic conditions, the quantity of free radicals that is generated is significantly reduced. Hypothermia has some anticoagulatory effects as well.

Numerous animal experiments have clearly demonstrated that key destructive processes of the neuroexcitatory cascade (such as calcium influx, accumulation of glutamate, and the release of its coagonist glycine) can be prevented, interrupted, or mitigated by hypothermia.²³ Hypothermia may decrease the area of cardiac injury, promote epicardial reflow, decrease myocardial metabolic demand, and preserve intracellular high energy phosphate stores.^{24,25}

ADVERSE EFFECTS OF INDUCED HYPOTHERMIA

Hypothermia is also associated with a number of adverse effects and complications,²⁶ which will have their impact on the status and outcome of the patient undergoing IH.

Cardiovascular

Considering the fact that almost 80% of the patients with cardiac arrest have a background of cardiac disease and almost 60% of the mortality in adults is due to coronary artery disease, they are more prone to hypothermia-induced cardiac dysfunction and hemodynamic imbalance.^{27,28}

Lower heart rate in hypothermia is due to the decrease in diastolic depolarization of sinoatrial node cells. Electro-

cardiographic changes, which are noted in IH include increased interval between different complexes (PR and QT) and also widening of the wave of ventricular depolarization (QRS), and sometimes, the presence of Osborn wave. Increased incidence of serious arrhythmias, when the core body temperature reaches about 28–30°C with concomitant electrolyte abnormalities may be troublesome. Moreover, hypothermic myocardium is resistant to antiarrhythmic drugs such as amiodarone and xylocaine.

Induced hypothermia induction increases catecholamine levels, thereby increasing cardiac output and metabolic demand of myocardium (cerebral metabolic rate of oxygen). This also shifts blood volume from the peripheral to the central circulation and also increases venous return causing sinus tachycardia. When the body temperature falls below 35.5°C, it causes sinus bradycardia, diastolic and systolic dysfunction leading to a 25% decrease in cardiac output. Central venous blood oxygen saturation remains unchanged or may increase due to decreased oxygen consumption in the peripheral tissues.²⁶

Myocardial ischemia in hypothermic patients depends on the previous status of coronary artery in patient, so that in normal individuals, hypothermia has been shown to improve myocardial blood flow; however, in patients with a history of coronary artery disease, it causes vasoconstriction in atherosclerotic arteries.²⁹ Recurrence of ventricular fibrillation would be dangerous for the patients, if moderate induced hypothermia (MIH) is initiated soon after ROSC.⁹

Coagulopathy

Induced hypothermia causes mild increase in bleeding tendency by affecting platelet number and function, production of clotting enzymes, and tissue plasminogen activator inhibitor enzyme.³⁰ Platelets become sequestered in the spleen and liver during hypothermia, and re-enter the circulation after rewarming. Coagulopathies associated with hypothermia would question the safety of the procedure in patients following revascularization of the coronary arteries with fibrinolytic medications or percutaneous coronary intervention.

Electrolytes

Increased renal excretion of electrolytes and the resulting intracellular shift lead to hypomagnesemia, hypokalemia, and hypophosphatemia. Magnesium deficiency is associated with cerebral and coronary vasoconstriction and adverse neurological outcomes. It also causes atrial and ventricular arrhythmias, bronchospasm, seizures, and metabolic effects such as insulin resistance. Magnesium deficiency can further augment hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia leading to further arrhythmias, muscle weakness, and neuromuscular disorders.²⁹ Magnesium supplementation is reported to prevent the damage caused by reperfusion. Hypophosphatemia causes weakness of the diaphragmatic and respiratory muscles, increased risk of respiratory infections, and delay in weaning the patient from the mechanical ventilator. Clinical effects of hypokalemia include cardiac arrhythmias, muscle weakness, rhabdomyolysis, renal failure, and elevated levels of blood sugar (due to suppression of insulin secretion). Both hyponatremia and hypernatremia may exacerbate brain injury.

Metabolic Disturbances

Insulin resistance and decreased insulin release contribute to hyperglycemia resulting in increased rate of infection, neuropathy, and renal failure. This situation calls for tight control of blood sugar levels.³¹

Renal Function

Cold diuresis is a major concern in patients with hypothermia. It occurs due to decreased reabsorption of the solutes in the ascending loop of Henle, and relative increase in venous return activates the secretion of atrial natriuretic peptide and reduces antidiuretic hormone levels. The reasons for the increased renal excretion also include changes in blood volume, cardiac preload, impaired tubular function, and increased blood viscosity (2% per 1°F degree fall).³² Left untreated, this leads to hypovolemia, electrolyte loss, and hemoconcentration, with ensuing complications.

Gastrointestinal Problems

Decreased gastrointestinal motility may require a prokinetic. While feeding rates are reduced to reflect lower metabolic demands, some protocols completely forbid feeding during IH. Serum amylase and liver enzymes are frequently raised and a metabolic acidosis also occurs as a result of increased lactate concentrations and increased production of free fatty acids, ketones, and glycerol. Rarely, these changes can be severe and pancreatitis can ensue.

Drug Metabolism

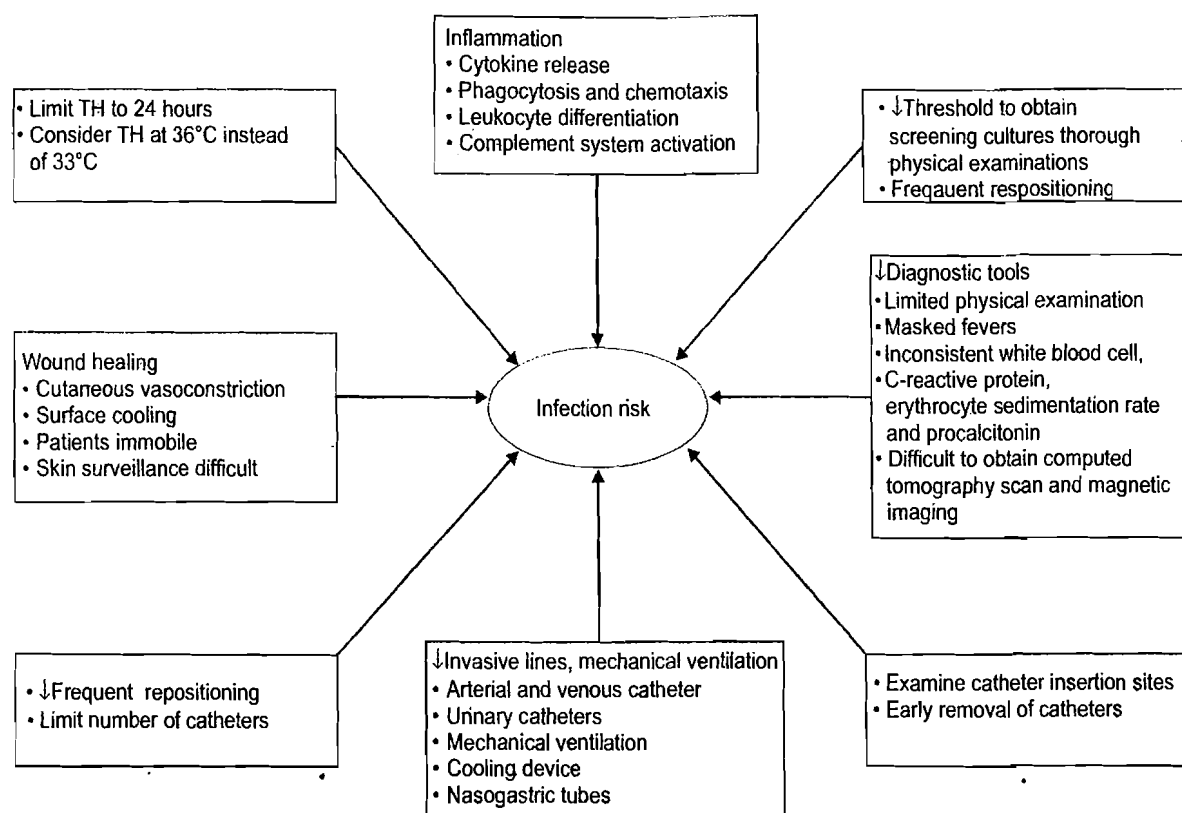
As most of enzymes activities are temperature dependent, IH nonspecifically lowers enzyme activity, leading to lower hepatic clearance and higher plasma levels of some drugs. The activity of enzymes, such as cytochrome P450, is reduced by 7–20% per 1°C fall in core temperature, leading to longer half-lives of circulating drugs, especially sedatives or anesthetics. Clearance of most drugs (propofol, muscle relaxants, fentanyl, and barbiturates) is reduced by hypothermia. The effects of most medications used in CPR could be decreased or delayed. Lidocaine has no confirmed effects throughout hypothermia. Amiodarone is also not useful in controlling fibrillation in the hypothermic heart. Hypothermia also blunts response of vasoactive drugs such as adrenaline and noradrenaline.

Sepsis

Hypothermia inhibits the secretion of cytokines and suppresses the migration of leukocytes and phagocytes (Fig. 2). Induced hypothermia may mask clinical signs of infection, such as fever, and it may impair the immune response to infection. Though several studies suggest a trend toward increased infections in IH, clinical implications of this are not clear.³³

Hypothermia After Cardiac Arrest researchers reported sepsis as the most important complication of MIH, though it was not statistically significant.^{10,34} A systemic review and meta-analysis³⁵ including 23 randomized controlled trials (RCTs) (n = 2,820) to investigate the risk of infection associated with IH, concluded that TH increases the risk of pneumonia and sepsis with no increase in overall risk of infection. Nosocomial pneumonia will occur in over half of patients who are hypothermic for more than 7 days.

Clinical studies with therapeutic cooling in settings in which selective decontamination of the digestive tract was used have reported low infection rates, even when hypothermia was used for prolonged periods.³⁶ Delayed wound healing will demand vigilant nursing care to prevent pressure sores. Regular surveillance of vascular device sites and other surgical wounds should be undertaken. Some protocols recommend daily blood surveillance cultures to screen for bacteremia. The threshold for antibiotic treatment is usually low.



WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CT, computed tomography; MRI, magnetic resonance imaging; MV, mechanical ventilation; TH, therapeutic hypothermia.

FIG. 2 Influence of induced hypothermia on immune function and factors affecting infection risk³⁴

Acid-base Measurements

In hypothermia, solubility of gases in blood increases, making patients appear to have respiratory alkalosis when arterial blood gas sample is adjusted to compensate for the low temperature.³⁷

PATIENT SELECTION FOR INDUCED HYPOTHERMIA

After more than 2 decades of trials and travails of IH for post-cardiac arrest ROSC patients, the following criteria for including and excluding patients have been evolved (Box 1 and Table 3). It is evident that while inclusion is very simple, the exclusion criteria limit several patients to have IH, when and if they are resuscitated from CA. These form the important barriers to implementation of IH in post-cardiac arrest patients.³⁸

Box 1: Patient selection for induced hypothermia

- Intubated patients with treatment initiated within a 6-h post-cardiac arrest (nonperfusing ventricular tachycardia or ventricular fibrillation)
- Those able to maintain a systolic blood pressure >90 mmHg, with or without pressors, after cardiopulmonary resuscitation
- Those in a coma at the time of cooling. Patients with brainstem reflexes, pathological posturing movements, and Glasgow Coma Score (GCS) of 3 are eligible for hypothermia

TABLE 3 Exclusion criteria for induced hypothermia

Clinical conditions	Reasons and implications
Obeying verbal command after ROSC	Futility
Recent major surgery within 14 days	Increased risk of infection and bleeding
Systemic infection and sepsis	IH inhibits immune function and further increase in risk of infection
Coma from other causes	Drug intoxication etc. not proved in studies
Known bleeding diathesis or with active ongoing bleeding	IH may impair the clotting system Patients may receive chemical thrombolysis, antiplatelet agents, or anticoagulants
Trauma with severe bleeding	IH may accelerate hemorrhage
Valid do not resuscitate order	Terminal illnesses
Time from resuscitation until initiation of cooling >360 min	Futility
Pregnancy	Not tested for safety

IH, induced hypothermia

INDUCED HYPOTHERMIA TREATMENT PROTOCOLS AND CONTROVERSIES

Post-ROSC, the patient is actively cooled by using an IH protocol for 24 hours to a goal temperature of 32–34°C. Though the goal is to achieve target temperature as quickly as possible, it is usually achieved within 3–4 hours of initiating cooling. Rewarming is begun 24 hours after the time of initiation of cooling, but more evidence is needed to define the optimal duration of hypothermia.

Timing of Cooling

It is understood that variables of timing of the initiation of cooling; cooling technique; rate, depth, and length of cooling; and rewarming all have some effect on mortality and morbidity. However, at this time, these variables are not well-studied and are the focus of several ongoing trials.

In a study evaluating the effect of time to target temperature (TTT) on neurological outcome, it was found that the outcome worsened for each 5 minutes delay in initiating TH at the time of discharge from intensive care unit, and for every 30 minutes delay at postdischarge follow-up.³⁹ Wolff et al. demonstrated good neurological outcome, as denoted by lesser hypoxic brain injury, after cardiac arrest, through achieving early hypothermia with the aid of endovascular cooling devices.⁴⁰

ARCT of prehospital intranasal cooling, Pre-Resuscitation Intra-Nasal Cooling Effectiveness (PRINCE) trial from 2010,⁴¹ found no significant differences in rates of ROSC, in overall survival, or in neurologically intact survival to discharge. Further, RCT by Kim et al. not only failed to prove any benefit in the form of survival or neurological outcome of successful prehospital cooling to 34°C, but also indicated towards increased harm in shape of rearrests and increased incidence of pulmonary edema, in both ventricular fibrillation and non-ventricular fibrillation arrests.¹²

Moritz Haug et al.⁴² in a retrospective observational study of 588 patients in an academic emergency department, calculated correlation of TTT with neurologic outcome in patients after cardiac arrest with ROSC, by treating with therapeutic mild hypothermia. Survival and neurological outcomes were determined within 6 months after cardiac arrest. The median time from restoration of spontaneous circulation to reaching a temperature of less than 34°C was 209 minutes [interquartile range (IQR): 130–302] in patients with favorable neurological outcomes compared to 158 minutes (IQR: 101–230) ($p < 0.01$) in patients with unfavorable neurological outcomes. They concluded that in comatose cardiac arrest patients treated with TH after ROSC, a faster decline in body temperature to the 34°C target appears to predict an unfavorable neurologic outcome.

Rewarming from Induced Hypothermia

Rapid rewarming may actually deprive the various protective benefits of IH, as evidenced by greater decrease of jugular venous oxygen saturation in comparison to lesser rapid rewarming.^{43,44} More importantly, maintaining normothermia during rewarming is mandatory, as fever is independently linked to adverse outcomes in post-cardiac arrest anoxic injury.⁴⁵ Release of potassium sequestered in intracellular compartment during hypothermia leads to rebound hyperkalemia during rewarming,⁴⁶ which can be prevented by slow and controlled rewarming. Renal replacement therapy should be initiated in patients with anuria or severe oliguria before rewarming.

Disagreements on Outcome of Induced Hypothermia

Moderate therapeutic hypothermia has been recommended by many societies for patients in coma with ROSC after resuscitation from out-of-hospital cardiac arrest due to “shockable rhythms”. Some of them have also extended this recommendation to similar situation after ROSC from other cardiac rhythms and after in-hospital cardiac arrest, which probably is responsible for the widespread use of TH. This is beyond the indications employed in the initial two RCTs. These recommendations were largely due to the results of some often quoted studies mentioned earlier in this chapter. Various authors reanalyzed these studies and have suggested that thoughtful consideration should be done before using IH universally.

The randomized evidence base that led to the 2003 ILCOR recommendation was based on a total of only 352 patients, just half of whom were randomized to TH. More than 95% had witnessed cardiac arrest, and the enrolment criteria stipulated either ventricular fibrillation or pulseless ventricular tachycardia as the presenting rhythm.⁴⁷

Zhang et al. meta-analyzed six RCTs and one abstract, and found that IH did not significantly decrease the mortality at hospital discharge [risk ratio (RR) = 0.92; 95% CI, 0.82–1.04; $p = 0.17$ at 6 months or 180 days (RR = 0.94; 95% CI, 0.73–1.21; $p = 0.64$)] in overall post-cardiac arrest, but it did reduce the mortality of patients with shockable rhythms at hospital discharge (RR = 0.74; 95% CI, 0.59–0.92; $p = 0.008$) and at 6 months or 180 days. Improvement in neurological outcome at hospital discharge (RR = 0.80; 95% CI, 0.64–0.98; $p = 0.04$) was seen in those with shockable rhythm but not at 6 months or 180 days. Complication rate was found to be more in patients who received IH compared to control group. Overall trial sequential analysis indicated lack of firm evidence for a beneficial effect.⁴⁸

Héssel 2nd et al.⁴⁹ believe that these recommendations need to be reassessed and evidence of the existing data is not strong enough. The AHA 2010 recommendation for

IH⁵⁰ is based on one RCT (level B evidence),¹⁰ one pseudo-randomized trial⁹ and two more studies with historical controls.^{51,52}

Walters et al.⁵³ systematically reviewed the studies on benefits of IH in post-cardiac arrest (40 uncontrolled observational studies, 24 nonrandomized trials, and 5 RCTs) and found that they have significant limitations such as methodological problems, risk of bias, and unblinded care teams.

Hypothermia After Cardiac Arrest Group study,¹⁰ which is by far the largest randomized study (273 patients) which showed mortality and neurological outcome benefits with IH, also has some limitations as pointed out by Neilsen et al.⁵⁴ and Testori et al.⁵⁵ For example, whereas the intervention group in this study was maintained strictly hypothermic up to 24 hours, the control group was allowed to drift into hyperthermia from 12th hour onwards, thereby turning the comparison into hypothermia versus hyperthermia and not versus normothermia.¹⁰

The often cited RCT (77 patients) of Bernard et al.⁹ from Australia, noted a better neurologic outcome (49 vs. 26%, RR 1.85, NNT 4; *p* value 0.046) and a lower mortality at discharge (51 vs. 68%, RR 0.76, NNT 6; *p* value 0.145) in unresponsive patients receiving TH after return of ROSC after shockable OOHCA. The better neurologic outcome (incidence of good outcome) was barely statistically significant (*p* = 0.046) and their observed lower mortality at discharge was not statistically significant at all (*p* = 0.145).

When Nielsen et al.⁵⁴ conducted a meta-analysis of the two RCTs of HACA trial¹⁰ and the Laurent trial,⁵⁶ they observed a reduced mortality [RR 0.92 (95% CI 0.56–1.51)] and improved neurologic outcome [RR 1.24 (95% CI 0.76–2.0)], which were not statistically significant.

Induced hypothermia after pulseless electrical activity (PEA), asystolic, or in-hospital arrest has not been fully studied. One large cohort study of cardiac arrest patients found that IH was not associated with good outcome in nonshockable patients.⁵⁷

Data from a study of prehospital hypothermia in 125 patients found that in those who had non-ventricular fibrillation arrest, i.e., PEA (*n* = 34), asystole (*n* = 39), or unknown rhythm (*n* = 1), survival to hospital discharge was worse in the cooled group (6%) than in the noncooled group (20%).⁵⁸ This study was not intended or powered to detect differences in clinical outcome at discharge, but it raises concern regarding the use of hypothermia in patients with PEA or asystole and ROSC with hypothermia in the prehospital setting.

The evidence for use of TH after in-hospital cardiac arrest is even less compelling. In the largest and most recent report by Nichol et al.⁵⁹ who employed propensity score adjustment for their outcome comparisons, IH was associated with statistically insignificant improvement in survival (OR 1.43; 95% CI 0.68–3.01) (Table 4).

It is clear that the data that has been produced regarding the benefit of IH in post-cardiac arrest situation has been interpreted differently by different groups. Walters et al.⁵³ in their systematic review concluded, “The extrapolation of the data from OOHCA associated with shockable rhythms to other cardiac arrests (e.g., other initial rhythms, in-hospital arrests, and cardiac arrests in children) seems reasonable but is supported by only lower level data. There is need for RCTs in these other groups”.

On the other hand, some more issues related to IH have remained unresolved, such as:

- Definite mechanism of action of IH
- What is more effective? Induced hypothermia or prevention of hyperthermia?
- Clear beneficiary and nonbeneficiary patient groups from IH
- Do nonshockable arrest patients really not benefit from IH?
- Induced hypothermia induction—early or late? Which is better?
- What is the optimum target temperature?

TABLE 4 Nonrandomized comparison of therapeutic hypothermia for in-hospital cardiac arrest

Author	Year	Reference	Study type	Patients (n)		Hospital survival (%)		Good neuro-outcomes (%)	
				Therapeutic hypothermia	Control	Therapeutic hypothermia	Control	Therapeutic hypothermia	Control
Arrich	2007	50	Multicenter observational European registry	43	59	39	60	28	29
Rittenberger	2004	51	Retrospective observational University of Pitt	13	27	14	14	8	7
Kony	2012	52	Retrospective historic Beth Israel	17	16	29	31	24	31
Nichol	2013	53	Multicenter prospective observational United States	214	8102	27.1	31.0	18.7	20.1

- Can we prognosticate the effect of IH in an individual patient?
- Does the technique used to achieve hypothermia matter?

Potential harms include infection, pneumonia, sepsis, hemodynamic instability, arrhythmias, hyperglycemia, coagulopathy, bleeding, electrolyte abnormalities, polyuria, seizures, and altered drug metabolism. Induced hypothermia is expensive, resource and labor intensive, diverts hospital resources, and it might give a false sense of hope to the family.

There are some unresolved issues, which include time window of therapeutic effectiveness, optimal method of inducing and maintaining IH, optimal temperature and duration period of hypothermia, rewarming process, temperature measurement details, proper sedation, analgesia and muscle relaxation, need for electroencephalographic monitoring, seizure detection and management, management of shivering, optimal hemodynamic goals, neurologic assessment and how to assess neurologic prognosis, and criteria for and when to withdraw life support.⁶⁰⁻⁶³

Nielsen et al.⁵⁴ reported four key factors that need to be further researched and clear guidance evolved. They are—speed of induction of hypothermia, duration of cooling, rapidity of rewarming, and management to prevent side effects of hypothermia.

CONCLUSION

Induced hypothermia continues to be an important component of modern postresuscitation care. In order to maximize the beneficial effect of IH, it should be customized to the resuscitation covariates and adapted to the patient's needs. In particular patients, who suffered a witnessed cardiac arrest, with preferably ventricular fibrillation as primary rhythm, a long-time period of circulatory standstill before initiation of resuscitation and an overall resuscitation time not exceeding 29 minutes might benefit from cooling to a target temperature of 32–34°C for 24 hours. To answer the question, if cooling during CPR or in the prehospital setting is indicated, additional adequately powered and well-performed studies would be necessary in the future.

The evidence refuting the benefits of IH is as weak as that which supports its use. However, based on the recommendations, practice of IH has become an established practice universally. The least that can be stated is that IH should not be used indiscriminately, in all postarrest situations. Consider implementing in-hospital cardiac arrest (32–34°C or <37°C) in patients with in-hospital cardiac arrest who are unconscious after ROSC and with favorable outcome with reversible causes of cardiac arrest.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6-e245.
2. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Consensus Statement from the International Liaison Committee on Resuscitation. *Circulation*. 2008;118(23):2452-83.
3. Polderman KH, Varon J. Cool hemodynamics—the intricate interplay between therapeutic hypothermia and the post-cardiac arrest syndrome. *Resuscitation*. 2014;85(8):975-6.
4. Dragancea I, Rundgren M, Englund E. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. *Resuscitation*. 2013;84(3):337-42.
5. Laver S, Farrow C, Turner D, et al. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med*. 2004;30(11):2126-8.
6. Hippocrates (460-375 BC). *De Vetere Medicina*. Jones WHS, Withington ET (Trans). Hippocrates. Germany: Loeb Classical Library.
7. Hegnauer AH, D'Amato HE. Oxygen consumption and cardiac output in the hypothermic dog. *Am J Physiol*. 1954;178(1):138-42.
8. Benson DW, Williams GR Jr, Spencer FC, et al. The use of hypothermia after cardiac arrest. *Anesth Analg*. 1959;38:423-8.
9. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Eng J Med*. 2002;346(8):557-63.
10. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-56.
11. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197-206.
12. Kim F, Nichol G, Maynard C, Hallstrom A, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. *JAMA*. 2014;311(1):45-52.
13. Testori C, Sterz F, Holzer M, et al. The beneficial effect of mild therapeutic hypothermia depends on the time of complete circulatory standstill in patients with cardiac arrest. *Resuscitation*. 2012;83(5):596-601.
14. Wallmuller C, Testori C, Sterz F, et al. Limited effect of mild therapeutic hypothermia on outcome after prolonged resuscitation. *Resuscitation*. 2015;98:15-9.
15. Stratil P, Holzer M. Is hypothermia indicated during cardiopulmonary resuscitation and after restoration of spontaneous circulation? *Curr Opin Crit Care*. 2016;22(3):212-7.
16. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the international liaison Committee on Resuscitation. *Circulation*. 2003;108(1):118-21.
17. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out of hospital cardiac arrest incidence and outcomes. *JAMA*. 2008;300(12):1423-31.
18. Hovdenes J, Laake JH, Aaberge L, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anaesthesiol Scand*. 2007;51(2):137-42.
19. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med*. 2006;34(12 Suppl):S490-4.
20. Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke*. 2006;37(7):1792-7.
21. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(Suppl 2):S465-82.
22. Negovsky VA. Post resuscitation disease. *Crit Care Med*. 1988;16(10):942-6.
23. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med*. 2009;37(7 Suppl):S186-202.
24. Grimes C, Anderson R, Horiuchi T, et al. Resuscitative hypothermia after cardiac arrest: Performance in a community hospital. *Chest*. 2005;128:167S-a.
25. Scott BD, Hogue T, Fixley MS, et al. Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. *Clin Cardiol*. 2006;29(12):525-9.

26. Soleimanpour H, Rahmani F, Goltzari SE, et al. Main complications of mild induced hypothermia after cardiac arrest: a review article. *J Cardiovasc Thorac Res*. 2014;6(1):1-8.
27. Nolan JP, Deakin CD, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2005. Section 4. Adult advanced life support. *Resuscitation*. 2005;67 (Suppl 1):S39-86.
28. Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104(18):2158-63.
29. Soleimanpour H, Rahmani F. *Mild induced hypothermia after cardiac arrest: Advent of a novel approach in cerebral resuscitation*, 1st edition. Tabriz: Cardiovascular Research Center, Tabriz University of Medical Sciences; 2013.
30. Milanovic R, Husedzinovic S, Bradic N. Induced hypothermia after cardiopulmonary resuscitation: possible adverse effects. *SIGNA VITAE*. 2007;2:15-7.
31. Kabon B, Bacher A, Spiss CK. Therapeutic hypothermia. *Best Pract Res Clin Anaesthesiol*. 2003;17(4):551-68.
32. Behringer W, Holzer M, Bernard S, et al. Prevention of postresuscitation neurologic dysfunction and injury by the use of therapeutic mild hypothermia. In: Paradis NA, Halperin HR, Kern KB, Wenzel V, Douglas A (Eds). *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*, 2nd edition. Cambridge, UK: Cambridge University Press; 2007. pp. 848-85.
33. Wolfrum S, Radke PW, Pischon T, et al. Mild therapeutic hypothermia after cardiac arrest—a nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. *Resuscitation*. 2007;72(2):207-13.
34. Kuchena A, Merkel MJ, Hutchens MP. Postcardiac arrest temperature management: infectious risks. *Curr Opin Crit Care*. 2014;20(5):507-15.
35. Geurts M, Macleod MR, Kollmar R, et al. Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):231-42.
36. Polderman KH, Tjong Tjin Joe R, et al. Effects of artificially induced hypothermia on intracranial pressure and outcome in patients with severe traumatic head injury. *Intensive Care Med*. 2002;28(11):1563-73.
37. Luscombe M, Andrzejewski JC. Clinical applications of induced hypothermia. *Contin Educ Anaesth Crit Care Pain*. 2006;6(1):23-7.
38. Behringer W. Prevention and therapy of postresuscitation neurologic dysfunction. *Curr Opin Crit Care*. 2008;14(3):305-10.
39. Sendelbach S, Hearst MO, Johnson PJ, et al. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. *Resuscitation*. 2012;83(7):829-34.
40. Wolff B, Machill K, Schumacher D, et al. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. *Int J Cardiol*. 2009;133(2):223-8.
41. Castreñn M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation*. 2010;122(7):729-36.
42. Haugk M, Testori C, Sterz F, et al. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. *Crit Care*. 2011;15(2):R101.
43. Maxwell WL, Watson A, Queen R, et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. *J Neurotrauma*. 2005;22(8):873-84.
44. Kawahara F, Kadoi Y, Saito S, et al. Slow rewarming improves jugular venous oxygen saturation during rewarming. *Acta Anaesthesiol Scand*. 2003;47(4):419-24.
45. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008;371(9628):1955-69.
46. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101-20.
47. Lim ETS, Wong ASL, Ahmed NSB, et al. Review of the clinical evidence and controversies in therapeutic hypothermia for survivors of sudden cardiac death. *Proceedings of Singapore Healthcare*. 2015;24(1):42-53.
48. Zhang XW, Xie JF, Chen JX, et al. The effect of mild induced hypothermia on outcomes of patients after cardiac arrest: a systematic review and meta-analysis of randomised controlled trials. *Crit Care*. 2015;19:417.
49. Hessel EA 2nd. Therapeutic hypothermia after in-hospital cardiac arrest: a critique. *J Cardiothorac Vasc Anesth*. 2014;28(3):789-99.
50. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122(18 Suppl 3):S768-86.
51. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation*. 2007;75(2):252-9.
52. Castreñn S, Cortés M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. *Rev Esp Cardiol*. 2009;62(7):733-41.
53. Walters JH, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: a systematic review. *Resuscitation*. 2011;82(5):508-16.
54. Nielsen N, Friberg H, Gluud C, Heritz J, et al. Hypothermia after cardiac arrest should be further evaluated—a systematic review of randomized trials with meta-analysis and trial sequential analysis. *Int J Cardiol*. 2011;151(3):333-41.
55. Testori C, Sterz F, Behringer W, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation*. 2011;82(9):1162-7.
56. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. *J Am Coll Cardiol*. 2005;46(3):432-7.
57. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? insights from a large registry. *Circulation*. 2011;123(8):877-86.
58. Kim F, Olsufka M, Longstreth WT Jr, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation*. 2007;115(24):3064-70.
59. Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? *Resuscitation*. 2013;84(5):620-5.
60. Chamorro C, Borralló JM, Romero MA, et al. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. *Anesth Analg*. 2010;110(5):1328-35.
61. Gaieski DF, Neumar RW, Fuchs B, et al. Haemodynamic management strategies are not explicitly defined in the majority of therapeutic hypothermia implementation studies. *Resuscitation*. 2012;83(7):835-9.
62. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. *Resuscitation*. 2013;84(10):1324-38.
63. Kamps MJ, Horn J, Oddo M, et al. Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature. *Intensive Care Med*. 2013;39(10):1671-82.

Quick Sequential Organ Failure Assessment: New Trigger for Rapid Response Teams

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INTRODUCTION

With the evolution of critical care services across the world, clinicians started realizing need for development of accurate and reliable methods for assessing illness severity and prognosis to allow for proper allocation of limited healthcare resources and rationale for early interventions.

NEED FOR QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT

There are several outcome prediction models that are currently available for use in clinical practice. Among them are Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), the Logistic Organ Dysfunction Score (LODS), and the Mortality Probability Model (MPM). These scores were derived and validated in large groups of critically ill patients admitted in intensive care unit (ICU) and mostly use extensive data both physiological and laboratory after ICU admission for calculation.

Situation outside ICU area especially in emergency department (ED) is different. It may not be possible to get all the data required for calculation of these scoring systems. The adaptation of ICU-based scoring systems to application in the ED has been studied by some investigators in past.^{1,2} These studies have found the predictive abilities of these scoring systems to be modest at best, and given that these scores are often complex and require special software to calculate, the utility of applying them in real time in the ED is limited.

Septic patients form a major part of ICU patient cohort and carry increased risk of mortality. Many of these patients present to ED initially and may spend significant amount of time there before being diagnosed and triaged to ICU. If not recognized and treated promptly, these patients carry high mortality. Hence, early recognition of sepsis is very important. Sepsis is a syndrome of physiological and biochemical

abnormalities, and our understanding of underlying pathobiology is still evolving. Since there is no gold standard diagnostic test for sepsis, sepsis definition has always used expert opinions to generate definition and criteria for diagnosis. The 1991 and 2001 definitions of sepsis were very confusing and nonspecific, which lead to many discrepancies in the reported incidences and observed mortality. With better understanding of the pathophysiology of sepsis, it has now been redefined as "life-threatening organ dysfunction due to a dysregulated host response to infection".³

The sepsis definition was changed to facilitate early identification and accurate quantification of the burden of sepsis by healthcare providers and also helps early management and triaging of these patients. In most ICUs, Sequential Organ Failure Assessment (SOFA) scores or LODS have been used to identify organ dysfunction in patients with infection. SOFA scores are used to quantify the organ dysfunction using the laboratory and clinical variables in ICU [partial arterial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ratio, platelet count, bilirubin creatinine, blood pressure or use of vasopressor and Glasgow coma scale] (Table 1).

An acute change in the total SOFA score of ≥ 2 points consequent to the infection is indicative of organ dysfunction and is associated with an inhospital mortality of $>10\%$. Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with an inhospital mortality of $>40\%$. However, it may be time consuming to evaluate all the six components of SOFA. It also requires laboratory measurements, which is not readily available especially in out of hospital settings.

Quick sequential organ failure assessment (qSOFA) is a quick bedside test to identify and risk stratify patients with sepsis in out-of-hospital, ED, and in general ward settings. It mainly focuses on blood pressure, mental status, and respiratory rate to identify patients with sepsis.

- Blood pressure <100 mmHg systolic (+1 point)
- Altered mental status (+1 point)

TABLE 1 Sequential Organ Failure Assessment score

	Score				
	0	1	2	3	4
Respiratory					
PaO ₂ /FiO ₂ mmHg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Cardiovascular					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine any dose	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Coagulation					
Platelets × 10 ³ μL	> 150	<150	<100	<50	<20
Liver					
Bilirubin mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Renal					
Creatinine mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output mg/day	–	–	–	<500	<200

MAP, mean arterial pressure; FiO₂, fraction of inspired oxygen; PaO₂, partial arterial pressure of oxygen

- Respiratory rate > 22/min (+1 point).

Patients with suspected infection are likely to have sepsis, if they have at least two of the above criteria.

VALIDATION OF QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT⁴⁻⁶

Seymour and his colleagues did a retrospective analysis of a large database of hospitalized patients in the United States to assess the predictive validity of the systemic inflammatory response syndrome (SIRS) criteria, qSOFA, SOFA score, and LODS score.⁴ They found that SOFA scores [area under the receiver operating characteristic curve (AUROC) 0.74] were better in predicting hospital mortality in ICU patients with suspected infection than SIRS criteria (AUROC 0.64) and was not very different from the more complex LODS score (AUROC 0.75). However, in patients with suspected infection outside the ICU, qSOFA had a statistically greater predictive validity (AUROC 0.81) as against SOFA (AUROC 0.79) and LODS (AUROC 0.76). Quick sequential organ failure assessment retained its predictive value for community and hospital infections under varied measurement conditions in academic and community hospitals in the United States and Germany. It was, however, statistically inferior compared with SOFA for patients in the ICU (AUROC 0.74 for SOFA and 0.75 for LODS as against 0.66 for qSOFA). It also had a statistically lower content validity as a measure of multiorgan dysfunction.

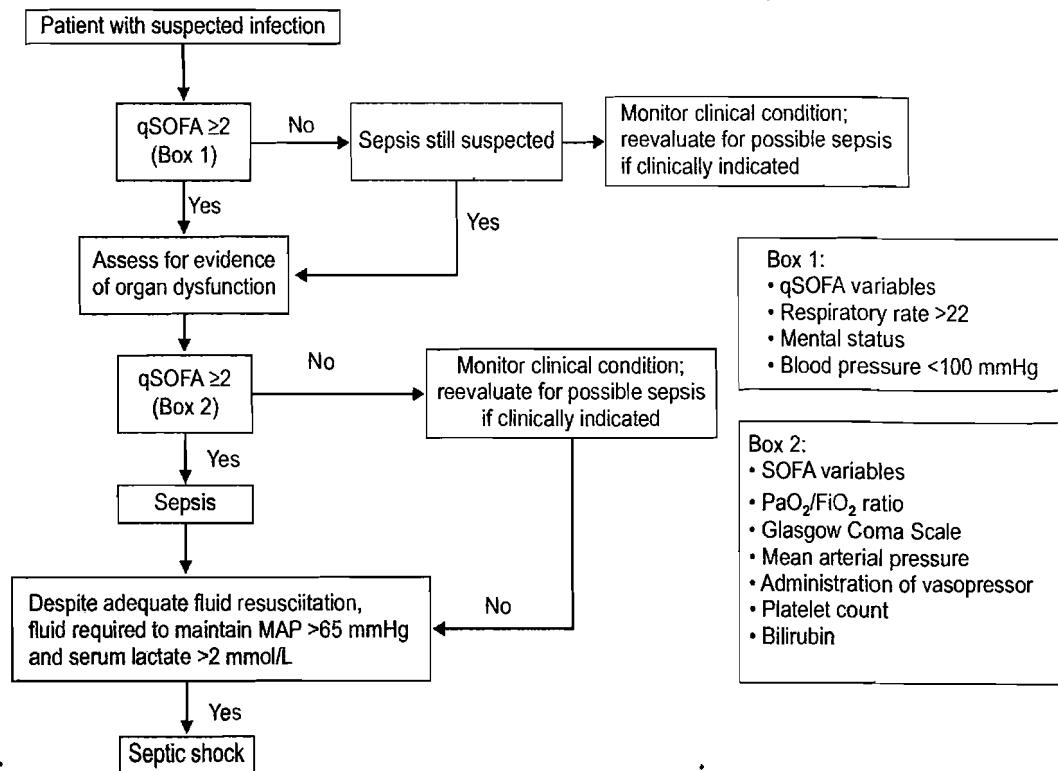
APPLICATION OF QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT

Quick sequential organ failure assessment can be useful as a rapid diagnostic tool especially in limited resource setting. However, qSOFA has not yet been externally validated in different healthcare settings. Hence, the current recommendations are to consider the possibility of sepsis, if the change in qSOFA is ≥2 in relation to infection. Since, it does not require any laboratory tests it can be performed quickly and repeatedly at the bedside. If the qSOFA criteria suggest that the patient is likely to have sepsis then it should prompt clinicians to further investigate the patient and initiate appropriate therapy or consider referral to critical care (Flowchart 1).

LIMITATIONS OF QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT

Firstly, qSOFA was derived and tested among patients in whom infection was already suspected. One has to remember that the qSOFA is not an alert that alone will differentiate patients with infection from those without infection.

Secondly, qSOFA is a mortality predictor and not a test to diagnose sepsis. Clinicians should be aware that positive qSOFA will be present with any type of shock, for example cardiogenic shock or obstructive shock. Hence, positive qSOFA should alert clinician to investigate patient further.



SOFA, sequential organ failure assessment; qSOFA, quick sequential organ failure assessment; MAP, mean arterial pressure; PaO₂, partial arterial pressure of oxygen; FiO₂, fraction of inspired oxygen.

FLOWCHART 1: Algorithm for identifying patients with sepsis and septic shock³

Thirdly, mental status is assessed variably in different settings, which may affect the performance of the qSOFA.

Fourthly one of the major causes of septic shock is pneumonia. CURB 65, recommended by British Thoracic Society is well validated simple scoring system used to prognosticate patients with community acquired pneumonia.⁶ CURB 65 includes confusion, urea above 7 mmol/L (>19 mg%), respiratory rate ≥30/min, systolic BP <90 mmHg or MAP ≤60 mmHg and age ≥65 years. Even in absence of blood urea CRB 65 can be used with equal efficacy. Superiority of qSOFA over well established CURB 65 in this patient subgroup needs to be established.

Also, clinicians have to be aware of the fact that abnormal qSOFA may be due to spurious abnormality, e.g., someone with low-baseline blood pressure or tachypnea due to anxiety. Patients may have abnormal qSOFA due to disease processes other than sepsis, e.g., patients presenting with chronic obstructive pulmonary disease exacerbation may be tachypnea or patients coming with stroke will have deranged mentation.

CONCLUSION

Quick sequential organ failure assessment is a simple bedside test, which can be used to identify and risk stratify

sepsis in patients outside the ICU. It is especially useful in resource-poor setting where laboratory investigations may not be readily available. However, one has to keep in mind it is not a test to diagnose presence of infection.⁶

REFERENCES

1. Jones AE, Fitch MT, Kline JA. Operational performance of validated physiologic scoring systems for predicting in-hospital mortality among critically ill emergency department patients. *Crit Care Med*. 2005;33:974-8.
2. Shapiro N, Howell MD, Bates DW, et al. The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection. *Ann Emerg Med*. 2006;48:583-90.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801-10.
4. Seymour CW, Liu V, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis. *JAMA*. 2016;315:762-74.
5. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:775-87.
6. Lim WS, Van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-82.
7. Vincent J, Martin G, Levy M. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care*. 2016;20:210.

Ventricular Preload Optimization Therapies: Science or a Dark Art?

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INTRODUCTION

Optimizing ventricular preload is an essential component in the care of critically unwell patients. In a range of clinical situations, including sepsis, trauma, perioperative patients, failure to undertake preload optimization, usually with the use of large volumes of intravenous fluids, is widely seen as suboptimal care. Several hemodynamic monitors have been developed and popularized for this purpose using pressure (central venous pressure or pulmonary artery wedge pressure), flow (aortic flow or cardiac output), volume (global end diastolic volume, intrathoracic blood volume), or direct imaging (ultrasound central venous collapsibility index) based parameters to optimize ventricular preload. More recently, sophisticated dynamic measurements such as stroke volume (SV) variation, pulse pressure variation, or systolic pressure variation either in response to a fixed volume of fluid challenge or maneuvers that recruit sequestered blood within various body compartments (straight leg raising test, Valsalva maneuver, etc.) have also been used to guide ventricular preload optimization. The basic physiological principle that underpins these clinical interventions is the Frank-Starling curve (Fig. 1).

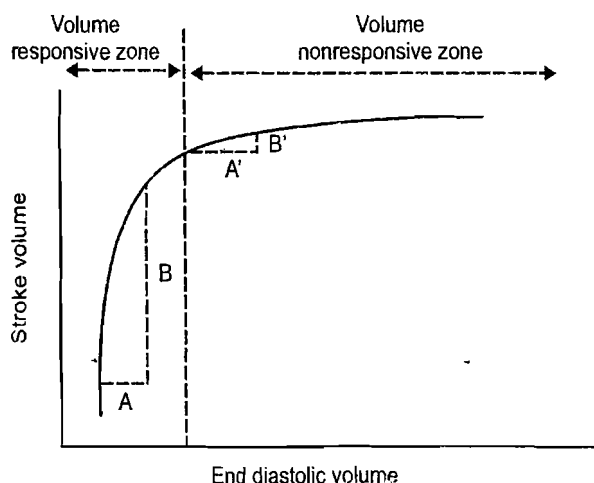


FIG. 1: Frank-Starling curve

The Frank-Starling curve, originally described by Otto Frank in 1895¹ and redescribed by Earnest Starling in 1914,² describes the relationship between the length of the sarcomere and the force generated by the cardiac myocytes during contraction. The clinical extrapolation of this original (experimental) description by Frank and Starling is the important relationship between end-diastolic volume and SV of the heart (Fig. 1), which is very frequently used to rationalize our current approach to fluid therapy and ventricular preload optimization. Using this approach, if the SV shows a substantial improvement (usually >10% increase) in response to the administration of repeated aliquots of fluid, it is assumed that the patient is within the volume-responsive region of the Frank-Starling curve (Fig. 1). In such patients, it is argued that further aliquots of fluid should be infused, so that the patient's end-diastolic volume is shifted rightwards toward the volume-nonresponsive portion of the curve. In other words, it is assumed that for optimal ventricular function, it is necessary to fill the ventricles to a point, where it is not volume responsive any further.

Experimental trials conducted in a range of clinical conditions seem to suggest that an aggressive, goal-oriented approach to fluid resuscitation—at least in the early stages of an evolving illness, such as severe sepsis, may improve survival and overall clinical outcome.³ Based on this rationale, several professional societies developed and popularized resuscitation algorithms that were quasi validated and subsequently adopted very widely across the world of intensive care medicine.⁴ “Fluids, more fluids, and even more fluids...” became the holy grail of resuscitation in order to optimize ventricular functions and, thereby improve oxygen delivery and tissue oxygenation. However, despite the initial enthusiasm generated by this approach, it soon became apparent that the findings reported in these early studies were not straightforward and not reproducible casting doubts on the underlying premise.⁵⁻⁶ Goal-directed therapy has also been developed for the cardiovascular management of patients in the perioperative setting.^{7,8} This approach has also failed to consistently show benefits in the hands of other

investigators, who attempted to reproduce the findings.⁹ It has even been argued that aggressive, goal-directed fluid resuscitation may benefit patients, if introduced before the onset of the injury/insult,¹⁰ but even in this context the results were not reproducible raising fundamental doubts on the entire approach.¹¹

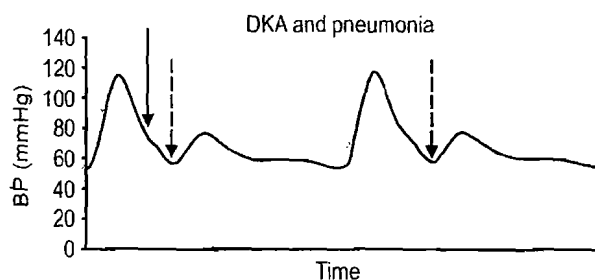
The counter point of view against this widely accepted dogma is that normal healthy human beings do not operate in the “fluid unresponsive zone” of the Frank-Starling curve. Perfectly healthy human beings living their ordinary lives and coping with a range of physiological and exercise-induced stress situations are all volume responsive. Kumar et al. in a landmark study administered a relatively large volume of isotonic saline to a group of 32 healthy volunteers. Their results show that the overwhelming majority of volunteers in their study showed an increase in SV in excess of 10% showing that they (healthy volunteers) were all operating within the volume-responsive zone of the Frank-Starling curve.¹² Similarly, the beat-to-beat variations in SV seen in healthy human beings during an ordinary spontaneous respiratory cycles or while performing the Valsalva maneuver (associated with the subtle changes in venous return and, therefore, the end-diastolic volumes) confirms that normal healthy human subjects in fact operate within the volume-responsive zone of the Frank-Starling curves.¹³ It is difficult to reconcile these observations in healthy volunteers with the current wisdom that recommend critically ill patients, including those with a potential for ischemic or sepsis-induced cardiac dysfunction, be managed within the “volume nonresponsive zone” of the curve and how such an “unphysiological” approach could confer survival benefits. Normal physiological parameters that are subject to positive and negative control mechanisms show substantial variation around a physiological “norm” and the absence or loss of these instantaneous and/or cyclical variations usually signify the loss of physiological adaptability and, hence, should be a marker of a maladaptive state or disease.^{14,15} In considering the merits of some of the landmark studies that have influenced the authors’ current practice,^{2,3,8,9,11} the possibility that the survival benefits demonstrated may have arisen as a result of inadvertent systematic bias or “placebo effect” built into the study designs (rather than being a true effect of the goal-directed treatment itself) needs further careful consideration. This may explain why the results from these positive studies—usually performed by the proponents of a given world view—have not always been reproducible by other, perhaps more cynical/skeptical, groups. Goal-directed treatment regimens will necessarily include greater attention by the attending clinical teams toward the treatment groups (in order to ensure the specific goals are being attained and maintained) and it is nearly impossible to determine what other advantages this greater attention by physicians concerned could confer on the treatment group within a complex environment such as the intensive care unit or the emergency department. In biological as well as physical systems, the process of “observation will

necessarily alter the phenomenon that is observed”, and it is important to bear this basic fact related to complex biological systems in mind when interpreting clinical trials that form the basis of popular algorithms and the recommended best practice. In this context, when clinical practice seems to be guided more by clinical trials rather than by any deeper understanding of the physiological systems that are at fault, it is necessary to revisit some of the abovementioned first principles, if further progress is to be achieved in the care of critically unwell patients.

Given this theoretical background, it seems prudent to ask how should fluid therapy be titrated or guided in critically unwell patients. There is no clear answer to this question and this is reflected in the continuing highly variable practice regarding fluid challenges in the critically ill.¹⁶ While acknowledging the fact that the true answer to this question still remains elusive, it seems reasonable to suggest that the first question to consider would be whether or not there is a physiological need for further fluid administration or circulatory volume expansion. In other words, the clinician at the bedside has to make an individualized clinical decision—based on history, clinical examination, and basic biochemical studies, if the current hemodynamic status is damaging to the overall well-being of that patient. This would require a comprehensive assessment of the patient concerned including the heart rate, capillary fill time, core temperature, mean arterial pressure, shape of the arterial pressure waveforms, current fluid balance, arterial lactate concentration, and urine output. It is only after such a comprehensive assessment of the overall clinical/hemodynamic status that a decision can be made, if the patient is currently in a truly compromised situation and, if further volume expansion could be of benefit in correcting this compromised status. No single number-based on any measured or calculated/derived hemodynamic variable can be reliable in answering the first question in this process, i.e., does this patient require more fluid? In this context, the current debates related to the relative merits of pressure, volume, and flow-based measurements are potentially misleading and at times a distraction.

ARTERIAL PRESSURE WAVEFORMS AND PATTERN RECOGNITION

In making a comprehensive assessment of a patient’s overall hemodynamic status as referred above, the arterial pressure waveforms transduced via a correctly positioned arterial cannula proves to be an extremely valuable adjunct. In addition to providing a beat-to-beat measurement of systolic, diastolic, and mean arterial pressures, particularly in situations where the above may change quite rapidly, the morphology of the waveforms can be used to glean several valuable clues on the overall status of the peripheral circulation. In this context, several characteristic patterns are commonly seen in critically unwell patients.



DKA, diabetes ketoacidosis; BP, blood pressure.

FIG. 2: Arterial pressure waveform in a patient with diabetes ketoacidosis and sepsis due to pneumonia

Figure 2 shows a real-time arterial pressure waveforms recorded in a septic patient. In a typical arterial waveform, the dicrotic wave—which is usually associated with the aortic recoil that occurs immediately following the closure of the aortic valve—is usually positioned two-thirds of the way down the descending limb of the pulse wave (solid arrow). In the presence of gross vasodilatation, as blood flows very rapidly into the peripheral circulation, the conditions necessary for the closure of the aortic valve (aortic root pressure more than ventricular luminal pressure) occurs later in the cardiac cycle compared to the normal subjects. This would be reflected by a delay in the onset of the dicrotic wave well beyond its usual position (interrupted arrow). In this particular patient, the delay is so profound that the dicrotic wave appears almost as a separate waveform arising from the baseline rather than the usual pattern, where it is seen as a wave arising from the downward limb of the main wave. This pattern is very typical of vasodilatation and is commonly seen in patients with sepsis, arteriovenous fistulae, general anesthesia or even in the presence of effective regional (epidural or spinal) blocks. In addition to the delayed dicrotic waves, such patients typically show a low-systolic pressure, a low-diastolic pressure and a wide pulse pressure as shown in figure 2.

How should one set out to achieve preload optimization in such a patient in whom there is profound vasodilatation? As mentioned in the previous section, there needs to be a clinical assessment to determine whether or not the current hemodynamic status needs to be corrected at all. This question can only be answered by a global assessment of the patient using history, clinical signs, hemodynamic status, and the biochemical picture, as described before rather than by any single number as suggested in many optimization algorithms. In such patients, with profound vaso- or venodilatation, a fluid challenge or a straight leg-raising test¹⁷ is most likely to show a significant increase in SV or one of its surrogate measurements. This increase in SV or one of its surrogates alone cannot be used to arrive at the conclusion that there is a need for further fluid administration. It is quite possible that hemodynamic optimization in such a patient with profound vasodilatation (if clinically indicated) may be better achieved through the initial administration of a vasopressor aimed at achieving some level of vasoconstriction, before further volume

expansion. Effective circulating blood volume is always an interplay between absolute blood volume and venous/arterial capacitance (or venous/arterial vessel tone) and the physiological interplay between the two variables has to be understood by the attending clinicians. In this context, the common algorithm driven approaches for patient management.

CONCLUSION

Over the past few decades, the practice of intensive care medicine has evolved into a discipline dominated by clinical trials, which then form the basis of treatment algorithms frequently with little consideration to the fact that what is true for a group of individuals (or a population) may not always hold true for any given individual within that population. In this journey, one may have come up with many dogmas and practices that do not always hold up to closer physiological or biological scrutiny. Ventricular preload optimization aimed at better ventricular performance, tissue perfusion and reduced myocardial oxygen consumption epitomizes many of these dogmas. Effective circulating blood volume is always an interplay between absolute blood volume and venous/arterial capacitance (or venous/arterial vessel tone) and the physiological interplay between the two has to be understood from first principles by clinicians who wish to manipulate these endpoints at the bedside. In doing so, despite all the recent advances in hemodynamic monitoring and treatment algorithms, one has to frequently fall back to the basics of clinical medicine in order to avoid the pitfalls that arise through focusing on isolated variables, numbers and dogmatic algorithms, inappropriately referred to as best practice.

REFERENCES

1. Frank O. Zur Dynamik des Herzmuskels. *Z Biol.* 1895;32:370-437.
2. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. *J Physiol.* 1914;48(5):357-79.
3. Rivers E, Nguyen B, Havstad S, Ressler J, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-77.
4. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* 2004;32(3):858-73.
5. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370(18):1683-93.
6. ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496-506.
7. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-11.
8. Noblett SE, Snowden CP, Shenton BK, et al. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg.* 2006;93(9):1069-76.
9. Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth.* 2005;95(5):634-42.

10. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014;311(21):2181-90.
11. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA*. 1993;270(22):2699-707.
12. Ziegler DW, Wright JG, Choban PS, et al. A prospective randomized trial of preoperative "optimization" of cardiac function in patients undergoing elective peripheral vascular surgery. *Surgery*. 1997;122(3):584-92.
13. Kumar A, Anel R, Bunnell E, Habet K, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med*. 2004;32(3):691-9.
14. Guz A, Innes JA, Murphy K. Respiratory modulation of left ventricular stroke volume in man measured using pulsed Doppler ultrasound. *J Physiol*. 1987;393: 499-512.
15. Godin PJ, Fleisher LA, Eidsath A, et al. Experimental human endotoxemia increases cardiac regularity: results from a prospective, randomized, crossover trial. *Crit Care Med*. 1996;24(7):1117-24.
16. Godin PJ, Buchman TG. Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med*. 1996;24(7):1107-16.
17. Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med*. 2015;41(9): 1529-37.
18. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med*. 2006;34(5):1402-7.

How to Assess and Improve Microcirculation?

JV Peter

INTRODUCTION

Circulatory shock is characterized by marked changes in hemodynamic parameters associated with evidence of organ dysfunction.¹ The traditional approach in shock was on macrocirculatory parameters that included cardiac output (measure of cardiac function), systemic vascular resistance (measure of vascular tone), and central venous pressure (measure of preload). It was observed that in some patients, despite "optimization" of these macrocirculatory (upstream) parameters, there was evidence of tissue hypoperfusion and progression of organ dysfunction.¹ This led to the revision of the definition of shock by the European Society of Intensive Care Medicine as "a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells."² This definition is more appropriate since the key factor appears to be alteration in cellular oxygen utilization at the microcirculatory level.³ Inadequate cellular oxygen utilization may occur in the setting of normal or increased cardiac output (e.g. septic shock) due to altered oxygen extraction (as a result of mitochondrial dysfunction) or reduced oxygen transport due to microvascular shunting resulting in inadequate oxygen delivery to the tissues and in situations of low cardiac output (e.g. cardiogenic and obstructive shock).³ Inadequate cellular oxygen utilization leads to cellular dysoxia with resultant increase in blood lactate levels, which further contributes to microcirculatory dysfunction.

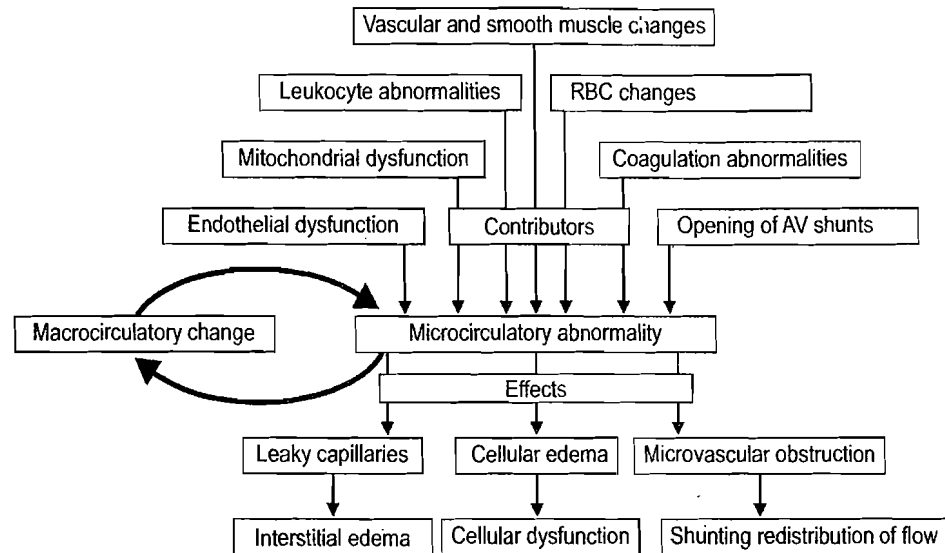
MICROCIRCULATORY FAILURE

Anatomically, the microcirculation is comprised of blood vessels $<100\ \mu\text{m}$ as well as the blood components, endothelium, and the glycocalyx.⁴ Functionally, the microcirculation is that part of the circulation where oxygen, nutrients, hormones, and waste products are exchanged between circulating blood and parenchymal cells.⁴ Recently, regulation and distribution of flow within the different

organs is also considered a function of the microcirculation.⁵ The microcirculation is controlled by local, mechanical, and endocrine factors.

Microcirculatory failure may occur directly as a result of a process that initiates microcirculatory abnormalities (e.g., sepsis and pancreatitis) or indirectly as a consequence of macrocirculatory failure (e.g., cardiogenic shock and obstructive shock).³ Although microcirculatory changes in circulatory shock are global, regional vascular beds may respond differently by either shunting of blood or vasodilatation. For example, regions such as the skin, muscle and splanchnic circulation may typically respond to the early phases of hypovolemic shock by vasoconstriction in order to increase mean-systemic filling pressure and maintain blood flow to more essential organs.³ It is also evident now, that in septic patients, there is a decrease in capillary density in the vascular bed associated with an increase in the heterogeneity of perfusion due to the presence of intermittently or nonperfused capillaries in close proximity to well-perfused capillaries.^{1,6-8} Moreover, this process appears to be dynamic, wherein capillaries in which there is no flow at a given time may be perfused a few minutes later.¹ Such heterogeneity of perfusion poses several challenges in the measurement of the "adequacy" of the microcirculation, unlike the measurement of macrocirculatory parameters, such as cardiac output and vascular resistance, which can not only be easily measured but also manipulated readily.

At a cellular level, many factors contribute to microcirculatory abnormalities (Flowchart 1). They include endothelial dysfunction, leukocyte activation, alterations in the hemorheological properties of red cells, coagulation abnormalities, vascular smooth muscle changes, and mitochondrial dysfunction that result in cellular edema, microvascular obstruction with shunting, leaky capillaries, and interstitial edema, that contribute to patchy heterogeneous areas of hypoxia and microcirculatory changes, characteristic of human sepsis.^{3,9,10}



RBC, red blood cell; AV, arteriovenous

FLOWCHART 1: Macrocirculatory changes may result in microcirculatory abnormalities in situations such as cardiogenic shock, where the primary problem is in the macrocirculation. However, in situations such as septic shock, primary microcirculatory changes lead on to macrocirculatory abnormalities. These microcirculatory abnormalities are contributed by endothelial and mitochondrial dysfunction, red cell and white cell abnormalities, changes in the vascular and smooth muscle function, coagulation abnormalities, and opening up of arteriovenous shunts. The effects of these are leaky capillaries with interstitial edema; cellular edema, which results in cell dysfunction and microvascular obstruction, which results in shunting and redistribution of flow

Under normal circumstances, heterogeneity of microcirculatory perfusion is minimal. In hypoxia or low-flow conditions, matching of perfusion to metabolism is done to some extent.¹¹ However, in sepsis, heterogeneity cannot be improved in response to changes in oxygen demand or to decreases in oxygen delivery. The heterogeneity of microvascular perfusion increases the oxygen diffusion distance and results in an extraction defect with increase in mixed venous oxygen saturation (SvO₂).¹¹

In clinical studies, impairment of microcirculation has been shown to be associated with mortality and organ dysfunction in patients with sepsis.¹⁰ In one study of 49 patients with septic shock, microcirculatory alterations were found to improve rapidly in septic shock survivors, but not in patients dying with multiorgan failure, regardless of whether shock had resolved or not.¹² In another study of 50 patients with septic shock, when compared with healthy volunteers, the density of all vessels and the proportion of perfused small vessels were significantly reduced in patients with sepsis.¹³ Microvascular blood flow alterations were more severe in patients with a worse outcome.¹³ In a more recent study of 25 patients with septic shock, similar findings in the microcirculation, as above, were observed in septic patients.¹⁴

ASSESSMENT OF THE MICROCIRCULATION

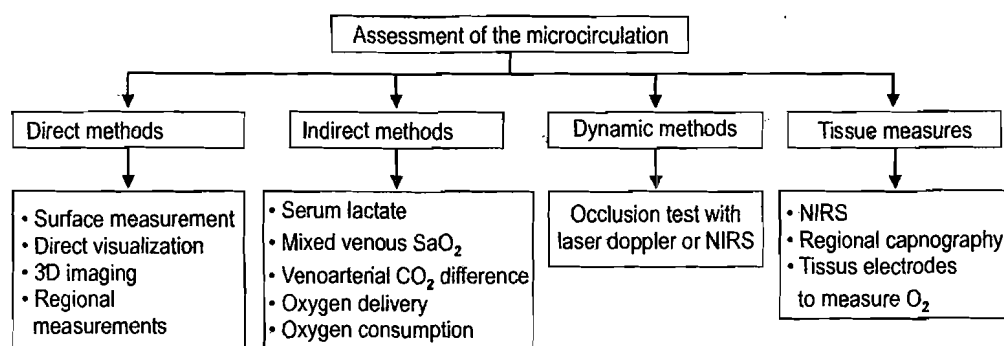
Prior to modulating or manipulating the microcirculation with various therapies, it is essential first to be able to develop objective and replicable tools to measure the adequacy or appropriateness of the microcirculation so that response to

therapy can be monitored and subsequently these responses can be correlated with clinically meaningful outcomes. The microcirculation can be assessed indirectly through surrogate downstream markers (such as lactate, oxygen delivery, etc.) or directly by methods that enable direct visualization of tissue perfusion (video microscopic techniques). In addition, direct measurement of tissue oxygenation as well as dynamic tests (e.g., occlusion test) help in the assessment of the microcirculation (Flowchart 2).

Indirect Downstream Parameters

Several downstream parameters have been evaluated and used in clinical practice. They include lactate, SvO₂, venoarterial carbon dioxide (vaCO₂) difference, measurements of oxygen delivery (DO₂) and oxygen consumption (VO₂), and tonometry.¹⁵

Lactate is the most widely studied downstream parameter that has been used as a marker of anaerobic metabolism and tissue hypoperfusion.¹⁶ Hyperlactatemia represents the imbalance between lactate production and clearance. Lactate levels in the critically ill can be influenced by other factors such as global hypoperfusion (circulatory shock and hypoxia), regional hypoperfusion (bowel or limb ischemia), drugs (metformin and catecholamines), mitochondrial dysfunction (sepsis and drugs), and hepatic dysfunction (decreased metabolism).¹⁷ These factors make it difficult to interpret lactate levels in the critically ill. Single estimates of lactate have not been shown to correlate with mortality. However, serial lactate measurements as well as lactate clearance overtime have been demonstrated to be



3D, three dimensional; CO₂, carbon dioxide; O₂, oxygen; NIRS, near-infrared spectroscopy; SaO₂, oxygen saturation.

FLOWCHART 2: The microcirculation can be assessed by (1) direct methods, (2) indirect methods, (3) dynamic methods and (4) measurement of tissue parameters. Direct methods include (A) surface measurements such as laser Doppler flux measurement, reflectance spectroscopy and sidestream dark-field imaging, (B) direct visualization that include standard intravital microscopy and orthogonal polarization microscopy, (C) 3D imaging using photon emission tomography, magnetic resonance imaging and contrast echocardiography and (D) regional measurements using catheter techniques and plethysmography. Indirect methods involve the measurement of biochemical parameters such as lactate, or measures of oxygen or carbon dioxide such as mixed venoarterial saturation, venoarterial carbon dioxide difference, oxygen delivery and oxygen consumption. Dynamic tests involve occlusion tests and then assessing the response of the microcirculation using laser Doppler or Near-infrared spectroscopy (NIRS). Tissue measures include the direct measurement of tissue oxygenation using platinum electrodes or measuring oxy- and deoxyhemoglobin in tissues using NIRS

prognostic.¹⁷ In a recent study, reduction in lactate level was more pronounced in survivors than in nonsurvivors.¹⁶

Mixed venous oxygen saturation, measured through a pulmonary artery catheter is thought to reflect the average oxygen saturation in all perfused microvascular beds. Since SvO₂ is technically more difficult to measure due to the need to place a pulmonary artery catheter, central venous oxygen saturation (ScvO₂) has supplanted SvO₂ measurements. A low ScvO₂ would indicate either a decrease in the oxygen delivery to the tissues or an increase in the tissue oxygen consumption or both.¹⁸ A high ScvO₂ on the other hand would reflect reduced oxygen utilization by the tissues. In clinical situations of a low ScvO₂, improving oxygen delivery by optimizing cardiac output has been used in resuscitation protocols such as the early goal-directed therapy.¹⁹ Studies, however, have failed to show a relationship between admission ScvO₂ levels and mortality,^{16,18} although ScvO₂ at 48 hours may predict outcome.¹⁸ Overzealous correction of ScvO₂ to supranormal levels can also worsen mortality in patients with preexisting hypoperfusion-induced organ injury.²⁰ Current evidence does not support a major role for ScvO₂ monitoring and guided therapy in patients admitted with septic shock.

Venoarterial carbon dioxide (CO₂) difference is another parameter that is used to assess the adequacy of the microcirculation. This came about because some patients, despite "normalization" of ScvO₂ (>70%) continued to have features of tissue hypoperfusion, manifested by an increase in the vaCO₂.²¹ Patients with a vaCO₂ gap of >6 mmHg may thus reflect a subgroup of patients who remain inadequately resuscitated.²¹ On the other hand, another subset of patients have a "low" CO₂ gap of <6 mmHg. These patients are likely to have impaired mitochondrial respiration, whereby inefficient production of CO₂, due to anaerobic metabolism,

results in a low CO₂ gap.¹⁶ These findings may be consistent with cytopathic dysoxia or regional microcirculatory abnormalities in sepsis.^{16,22} In a recent study on patients with sepsis, those with normalized ScvO₂ and narrow vaCO₂ had increased mortality.¹⁶ In another study, vaCO₂ differences were shown to reflect microcirculatory alterations (as assessed by sublingual microcirculatory images) in patients with septic shock.²³

Other parameters that are used to monitor the microcirculation include VO₂ and DO₂. The VO₂/DO₂ dependence has been demonstrated to be a marker of tissue hypoxia and is associated with a poor outcome.²⁴ In experimental conditions, plasma hyaluronan levels have also been shown to be associated with impaired microcirculation in sepsis and therapies that improved the microcirculation also resulted in a decrease in hyaluronan levels.²⁵

Tissue dysoxia can also be assessed by regional intestinal capnography.¹⁵ This method measures the difference between intestinal partial pressure of carbon dioxide (pCO₂) and arterial pCO₂ and uses the principle of CO₂ diffusion from local anaerobic production across tissues and cell membranes.¹⁵ Gastric intramucosal pCO₂ values also correlated with sublingual pCO₂. Baseline difference between sublingual pCO₂ and arterial pCO₂ is a better predictor of survival than changes in lactate or SvO₂.²⁶

Measurement of Tissue Oxygenation

Tissue oxygenation [partial pressure of oxygen (PO₂)] can be assessed by the placement of multiple platinum electrodes of 15 µm diameter.²⁷ These electrodes, however, are sensitive to the highest PO₂. This test detects only global decrease in tissue oxygenation and is unable to detect PO₂ heterogeneity or regional decreases in tissue oxygenation.

Near-infrared spectroscopy (NIRS) is another test that uses near-infrared light to measure oxy- and deoxyhemoglobin in tissues. It is generally applied on the muscle. As with other tests, NIRS is able to provide only an aggregate of oxygen saturations in the sampling volume.²⁷

Direct Methods of Assessment of Microcirculation

These methods allow direct visualization of tissue perfusion. It must be kept in mind that measurement of microcirculation at a specific site may not be representative of global microcirculatory abnormalities, since regional differences as well as heterogeneity of flow in a specific site may occur in the same individual at different time points in the course of sepsis, as alluded to earlier. However, these methods have helped to better understand the changes that occur in the microcirculation as well as response to therapy.

Direct methods of assessment of microcirculatory abnormalities include: (i) surface measurements [e.g., laser Doppler flux measurement, reflectance spectroscopy and sidestream dark-field (SDF) imaging], (ii) direct visualization (e.g., standard intravital microscopy and orthogonal polarization microscopy), (iii) three-dimensional (3D) imaging (e.g., photon emission tomography, magnetic resonance imaging, and contrast echocardiography), and (iv) regional measurements (e.g., catheter techniques and plethysmography).²⁸ Regional measurements using 3D techniques in the critically ill are limited by cost as well as the challenges of transporting a critically ill for the procedure. Surface measurement techniques and direct visualization are commonly used in this setting.

Laser Doppler

It involves the principle of detection of frequency shift in laser light after it encounters flowing erythrocytes.²⁹ It measures the velocity of microcirculatory flow in a small area of microcirculation being an average of the velocities of all the vessels present in a measured volume.²⁹ The drawback of this technique is that it needs to be applied to the organ and, hence, its use is restricted to easily accessible organs such as the skin and mucosa. As described earlier, the skin responds early to circulatory shock with vasoconstriction; its microcirculation is also easily manipulated by vasoconstriction (either with drugs or with temperature) and, hence, its application in the skin to ascertain global microcirculatory abnormalities is fraught with problems. It has also been used recently to measure flow in the gastric mucosa, rectum, and vagina. Newer developments of this technology, such as speckle laser and confocal lenses, are being evaluated in experimental models.²⁷

Video-microscopic Techniques

These techniques involve the application of small microscopes to tissues to directly visualize microvessels.²⁷ Nailfold microvideoscropy was the first method used. However, its use is restricted due to it being affected by several factors that affect blood flow to the skin. Orthogonal polarization spectral (OPS) and later SDF imaging have been introduced.^{15,27} An OPS creates high-contrast images without the use of fluorescent dyes, contrast being obtained by the absorption of linearly polarized light by the hemoglobin in the blood.¹⁵ Data is recorded on a digital video recorder. The SDF is also based on the principle that light is absorbed by the hemoglobin. Several light-emitting diodes are positioned at the outer surface of the objective, isolated from the inner image-conducting core, so that the light reflected by the outer surface cannot enter the image conducting core.²⁷ These devices were initially studied in the nailbed; however, it can be used in mucosal surfaces such as the sublingual area. Its application is being considered to other accessible mucosal surfaces such as ileostomy, colostomy, rectal, and vaginal mucosa.²⁷ The modalities do not provide exact measurements of red blood cell flow velocity in individual vessels. Tissue perfusion is assessed using semiquantitative assessment with a score based on an average score of a maximum of 12 quadrants, derived from the overall flow impression of all vessels within a particular range of diameter in a given quadrant.²⁹ Although this technique is time-consuming, it is probably one of the best available modalities for assessment for tissue perfusion.²⁷ Compared to OPS, SDF offers the advantage of improved image quality, relative technical simplicity, and lack of need of a high-powered light source.²⁹ The disadvantages of both these techniques are movement and pressure artifacts or secretions that may influence the images.¹⁰ It also needs considerable experience as it is examiner-dependent.¹⁰

Dynamic Tests (Occlusion Tests)

Occlusion tests can be conducted with laser Doppler as well as NIRS devices. This test assesses the microvascular and tissue response to hypoxia. This is based on the observation that vasoreactivity is altered in patients with sepsis.²⁷ Transient arterial occlusion is applied to the arm by the placement of a cuff. The speed of flow (in the case of laser Doppler) or SO_2 recovery (in the case of NIRS) is assessed. It must, however, be remembered that the recovery slope is also influenced by tissue O_2 consumption and microvascular hemoglobin content and mechanical properties of the vessels.²⁷ However, these tests offer promise in the evaluation of the microvasculature.

SHOULD WE TARGET THE MICROCIRCULATION?

There are several studies that have shown that impairment of microcirculatory perfusion is associated with worsening organ dysfunction and increased risk of death.^{13,15,30,31} Thus it is logical that improvement in the microcirculation might result in improved outcome. De Backer et al. showed that sublingual microcirculatory perfusion was compromised to a greater extent in nonsurvivors than survivors of septic shock.¹³ These changes were in terms of a decrease in vessel density and an increased proportion of nonperfused or intermittently perfused capillaries.³⁰ In another study of 252 patients with severe sepsis, the same authors showed that microcirculatory alterations are stronger predictors of outcome than global hemodynamic variables.³¹ The authors also showed that microcirculatory perfusion improved overtime in survivors, whereas in nonsurvivors, these abnormalities persisted. It was also noted that the microcirculatory abnormalities could be fully reversed by the topical application of acetylcholine.³⁰ These studies suggested that the local epithelium was still responsive to nitric oxide, whereas vasoplegia due to ongoing sepsis was persistent.¹⁵

In a more recent international study published in 2015 involving 36 intensive care units and 501 patients, an abnormal microvascular flow index was present in 17% of patients.³² Microvascular abnormalities in this study were not associated with mortality. However, in patients with tachycardia, an abnormal microvascular flow index was independently associated with increased risk of death.³² These suggest that it may be worthwhile manipulating the microcirculation.

IMPROVING THE MICROCIRCULATION

Since the microvascular alterations in sepsis is heterogeneous, it is probably more important to recruit the microcirculation than to try and increase the total flow to the organ.¹ Since significant macrocirculatory abnormalities can contribute to microcirculatory abnormalities, it is important to also look at what may be the minimum macrocirculatory goals that should be achieved in order to optimize microcirculatory targets. The main goals in the macrocirculation are hemodynamic (blood pressure) and fluid (volume status). Thus, fluids and vasoactive agents are the key components of hemodynamic resuscitation with the objective of improving tissue perfusion as well as oxygenation.

The ideal blood pressure in circulatory shock is difficult to establish.³³ Dubin et al. evaluated the microcirculation of 20 patients with septic shock with a mean blood pressure of 65 mmHg. They observed that despite an increase in the mean blood pressure to 75–85 mmHg with noradrenaline, there was no significant increase in microcirculatory parameters.³⁴ It thus appears that achievement of macrocirculatory targets may not necessarily translate to improvements in the

microcirculation. This does not rule out the dependence of the microcirculation on the macrocirculation. The effects of intra-aortic balloon pump and extracorporeal membrane oxygenators have been recently studied.³⁵ Some changes in the microcirculation were observed following implantation of these devices, suggesting that when global perfusion is severely impaired it has an effect on the microcirculation, which can be partially ameliorated by improving the macrocirculation.³⁵

Fluid therapy is an important dimension of treatment, since it is likely to not only improve the volume status (the preload) but also help to optimize cardiac output as well as tissue perfusion. Observational studies have shown that administration of saline or albumin in septic patients results in an improvement in the microcirculation that is independent of cardiac output and mean arterial pressure.^{1,36,37} These effects were evident in the early phase (<24 h) of sepsis rather than in the late phase of sepsis.³⁶ There is still no consensus as to which fluid may be better in improving the microcirculation. Although theoretically colloids may be better than crystalloids, the former may contribute to an increase in the viscosity. There is also the suggestion that the effect of fluid therapy on microcirculation may be saturable with benefits in the early part of sepsis with no response subsequently.¹ The mechanism by which fluids may improve microcirculation is not clear; changes in viscosity, decreased cell adhesion, and decrease in vasoconstrictor substances are postulated mechanisms.¹

Red cell transfusion may have a beneficial effect on tissue perfusion and oxygenation by improving flow as well as increased oxygen carrying capacity. However, in patients with sepsis, trials have failed to show a benefit. While transfusions did improve the microvascular perfusion in those with severely altered microcirculation, in those with normal microcirculatory parameters, it tended to worsen microcirculation.^{1,38,39}

Although theoretically, vasopressors may reduce tissue perfusion by causing vasoconstriction, correction of hypotension with these agents results in improvement in microcirculatory parameters probably as a result of an increase in the perfusion pressure.¹ As observed earlier, higher blood pressure targets are not necessary to improve microvascular parameters. There is also promise in the use of β -adrenergic agents, which have been shown to improve microvascular perfusion. These effects were found to be independent of systemic effects. Similar effects are seen with milrinone and levosimendan.¹

Vasodilators are the class of drugs that have been most studied as potential agents to improve the microcirculation. This is because of the postulate that local constriction-dilatation regulates blood flow through the microcirculation.¹ A decrease in vascular density could be attributed to vasoconstriction. This came about from observations that topical application of acetylcholine resulted in improved flow in the microcirculation.³⁰ It was also observed

that nitroglycerin administration was associated with improvement in microcirculatory parameters. However, this finding has not been consistently demonstrated.³⁵ This is probably because of the heterogeneity of patients that were enrolled in the studies and the lack of selectivity of the agent on the vascular bed. This can result in vasodilatation of both perfused and nonperfused areas, resulting in excess flow in perfused areas and possibly reduction in flows in already low-perfused needy areas.¹

The role of dobutamine has been explored in some studies.^{10,40,41} De Backer et al. reported an improvement in the microcirculatory parameters in patients with septic shock.⁴¹ These effects were independent of the effects on the macrocirculation. However, in another study, despite improvement in macrocirculatory parameters, dobutamine was not associated with improved microcirculatory parameters.⁴⁰

Steroids and anticoagulants have shown some promise in improving microcirculation. Steroids, which are often used in patients requiring high dose inotropes, have been shown to help improve vascular tone, which in turn may alter capillary perfusion.³⁵ In one study of 20 patients with septic shock, there was a slight improvement in microcirculation with steroids within an hour of hydrocortisone administration, which was independent of arterial pressure. Anticoagulants may potentially improve microcirculation.^{10,35} Activated protein C has been shown to improve sublingual microperfusion in patients with severe sepsis. These effects may also be seen with antithrombin. However, the mechanisms are still unclear and needs further assessment.¹⁰

CONCLUSION

Despite the pitfalls and limitations in the assessment of the microcirculation, it appears that in future, accurate assessment and modulation of the microcirculation would be an important dimension of care in patients with septic shock. The heterogeneity of not only the microcirculation but also regional vascular beds poses tremendous challenges in the evaluation of microcirculatory abnormalities. Vasoactive agents that are currently available do not have selective action on regional vascular beds enough to improve perfusion to regions that are underperfused. Further work is required to translate these observations to improvements in clinically meaningful outcomes.

REFERENCES

- De Backer D, Orbeago Cortes D, et al. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence*. 2014;5(1):73-9.
- Cecconi M, Backer DD, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care medicine. *Intensive Care Med*. 2014;40(12):1795-815.
- Peter JV, Pulicken M. Hypotension and shock. In: David S (Eds). *Clinical Pathways in Emergency Medicine*. 1st ed. Springer: India; 2016. pp. 179-90.
- Piagnerelli M, Ince C, Dubin A. Microcirculation. *Crit Care Res Pract*. 2012;2012:867176.
- Hernandez G, Bruhn A, Ince C. Microcirculation in sepsis: new perspectives. *Curr Vasc Pharmacol*. 2013;11(2):161-9.
- Farquhar I, Martin CM, Lam C, et al. Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. *J Surg Res*. 1996;61(1):190-6.
- Verdant CL, De Backer D, Bruhn A, et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. *Crit Care Med*. 2009;37(11):2875-81.
- Secor D, Li F, Ellis CG, Gross PL, et al. Impaired microvascular perfusion in sepsis requires activated coagulation and P-selectin-mediated platelet adhesion in capillaries. *Intensive Care Med*. 2010;36(11):1928-34.
- Vincent JL, Ince D, Bakker J. Circulatory shock—an update: a tribute to Professor Max Harry Weil. *Critical Care*. 2012;16(6):239.
- Saugel B, Trepte J, Reuter DA. Macro- and microcirculation in systemic inflammation: an approach to close the circle. In: Vincent JL (Eds). *Annual Update in Intensive Care and Emergency Medicine*. 1st ed. Switzerland: Springer Publishing; 2014. Pp 325-39.
- De Backer D, Ospina-Tascon G, Algado D, et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med*. 2010;36(11):1813-25.
- Sakr Y, Dubois MJ, De Backer D, et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004;32(9):1825-31.
- De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med*. 2002;166(1):98-104.
- Edui VS, Enrico C, Laviolle B, et al. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. *Crit Care Med*. 2012;40(5):1443-8.
- Spronk PE, Zandstra DF, Ince C. Bench-to-bedside review: Sepsis is a disease of the microcirculation. *Crit Care*. 2004;8(6):462-8.
- Mahajan RK, Peter JV, John G, et al. Patterns of central venous oxygen saturation, lactate and veno-arterial CO₂ difference in patients with septic shock. *Indian J Crit Care Med*. 2015;19(10):580-6.
- Okorie ON, Dellinger P. Lactate: Biomarker and potential therapeutic target. *Crit Care Clin*. 2011;27(2):299-326.
- Varpula M, Tallgren M, Saukkonen K, et al. Hemodynamic variables related to outcome in septic shock. *Intensive Care Med*. 2005;31(8):1066-71.
- Rivers E, Nguyen B, Haystad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-77.
- Textoris J, Fouche L, Wiramus S, et al. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. *Crit Care Med*. 2011;15(4):R176.
- Vallee F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med*. 2008;34(12):2218-25.
- Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: Please "mind the gap!" *Intensive Care Med*. 2013;39(9):1653-5.
- Ospina-Tascon GA, Umana M, Bermudez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? *Intensive Care Med*. 2016;42(2):211-21.
- Monnet X, Julien F, Ait-Hamou N, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. *Crit Care Med*. 2013;41(6):1412-20.
- Marechal X, Favory R, Joulin O, et al. Endothelial glycocalyx damage during endotoxemia coincides with microcirculatory dysfunction and vascular oxidative stress. *Shock*. 2008;29(5):572-6.
- Marik PE, Bankov A. Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. *Crit Care Med*. 2003;31(3):818-22.
- De Backer D, Donadello K, Cortes DO. Monitoring the microcirculation. *J Clin Monit Comput*. 2012;26(5):361-6.
- Pries AR. Microcirculation: assessment techniques. [online] Available from: www.hemorreologia.com. [Accessed September, 2016].

29. Tyagi A, Sethi AK, Girotra G, et al. The microcirculation in sepsis. *Indian J Anesth.* 2009;53(3):281-93.
30. Chierego M, Verdant C, De Backer D. Microcirculatory alterations in critically ill patients. *Minerva Anesthesiol.* 2006;72(4):199-205.
31. De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. *Crit Care Med.* 2013;41(3):791-9.
32. Vellinga NA, Boerma EC, Koopmans M, et al. International study on microcirculatory shock occurrence in acutely ill patients. *Crit Care Med.* 2015;43(1):48-56.
33. Penna GL, Salgado DR, Japiassu AM, et al. Microcirculatory assessment: a new weapon in the treatment of sepsis? *Rev Bras Ter Intensiva.* 2011;23(3):352-7.
34. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow; a prospective study. *Crit Care.* 2009;13(3):R92.
35. De Backer D, Ortiz JA, Salgado D. Coupling microcirculation to systemic hemodynamics. *Curr Opin Crit Care.* 2010;16(3):250-4.
36. Ospina-Tascon G, Neves AP, Occhipinti G, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med.* 2010;36(6):949-55.
37. Pottecher J, Derudder S, Teboul JL, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. *Intensive Care Med.* 2010;36(11):1867-74.
38. Sakr Y, Chierego M, Piagnerelli M, et al. Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med.* 2007;35(7):1639-44.
39. Sadaka F, Aggu-Sher R, Krause K, et al. The effect of red blood cell transfusion on tissue oxygenation and microcirculation in severe septic patients. *Ann Intensive Care.* 2011;1(1):46.
40. Hernandez G, Bruhn A, Luengo C, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. *Intensive Care Med.* 2013;39(8):1435-43.
41. De Backer D, Creteur J, Dubois MJ, et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med.* 2006;34(2):403-8.

How to Interpret Venoarterial Partial Pressure of Carbon Dioxide?

Sheila N Myatra, Vikas Bhagat

INTRODUCTION

Early identification and adequate resuscitation for tissue hypoperfusion are key factors in the management of patients with shock.¹ Although early resuscitation seems to improve outcomes in severe sepsis and septic shock, the relative value of resuscitation goals continues to be highly debated.^{2,3} During the last decade, parameters such as stroke volume, stroke volume variation, central venous saturation of oxygen (ScvO₂), and cardiac index (CI) have been increasingly used to monitor adequate hemodynamic treatment. Monitoring of ScvO₂ is widely recommended²⁻⁴ although strongly challenged by some.^{5,6} In an early trial, Rivers, et al.³ observed a significant decrease in mortality when they used a resuscitation bundle targeting ScvO₂ >70%. Conversely, recent data failed to confirm any benefit with this approach.⁷ It has recently been shown that a supranormal high ScvO₂ (>80%) in septic patients correlates with a higher mortality compared to patients with normal ScvO₂ possibly due to microcirculatory hypoperfusion.^{3,8} The current dilemma faced by clinicians in resuscitation is in patients with normal ScvO₂ who supposedly are well resuscitated, but have occult global microcirculatory dysfunction, which if not corrected may lead to oxygen debt and organ failure. This issue is important as splanchnic hypoperfusion is associated with a mortality rate ranging from 15% to 63%.⁹ The mixed venous-to-arterial partial pressure of carbon dioxide difference [pmvCO₂ - arterial CO₂ tension (paCO₂) or ΔpCO₂] might help to address this problem and could serve as an additional parameter, which is easy to assess and routinely available to evaluate the adequacy of macro- and microcirculation. A mixed venous-arterial pCO₂ difference (ΔpCO₂) >5-8 mmHg in perioperative and intensive care settings has been associated with compromised macro- and microcirculatory function in numerous studies of septic patients.¹⁰⁻¹⁴

PHYSIOLOGICAL BACKGROUND

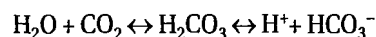
Carbon dioxide (CO₂) is transported in blood in three forms: (i) dissolved in solution, (ii) as bicarbonate, and (iii) with proteins in the form of carbamino compounds. The sum of all three forms is the total CO₂ content of blood.

Dissolved Carbon Dioxide

Carbon dioxide is more soluble in blood than oxygen (O₂) with a solubility coefficient of 0.031 mmol/L/mmHg (0.067 mL/dL/mmHg) at 37°C.

Bicarbonate

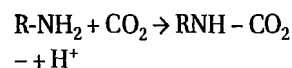
In aqueous solutions, CO₂ slowly combines with water to form carbonic acid and bicarbonate, according to the following reaction, which is accelerated by the enzyme carbonic anhydrase within erythrocytes and endothelium.



Less than 1% of the dissolved CO₂ in plasma undergoes this reaction and bicarbonate represents the largest fraction of the CO₂ in blood. The chloride shift is phenomenon related to differential shift of chloride in exchange of bicarbonate in the blood in the venous circulation and alveolar capillaries.

Carbamino Compounds

Carbon dioxide can react with amino groups on proteins, as shown by the following equation:



At physiological pH, only a small amount of CO₂ is carried in this form, mainly as carbaminohemoglobin. Deoxygenated hemoglobin (deoxyhemoglobin) has a greater affinity (3.5 times) for CO₂ than does oxyhemoglobin. As a result, venous blood carries more CO₂ than does arterial blood (Haldane effect). Partial pressure of carbon dioxide normally has little effect on the fraction of CO₂ carried as carbaminohemoglobin.

CARBON DIOXIDE DISSOCIATION CURVE

A CO₂ dissociation curve can be constructed by plotting the total CO₂ content of blood against pCO₂. The contribution of each form of CO₂ can also be quantified in this manner.

The relationship between the pCO₂ and the total pulmonary capillary oxygen content (CcO₂) is curvilinear although more linear than the oxygen dissociation curve. The pCO₂/CcO₂ relationship is influenced by hematocrit, peripheral capillary O₂ saturation, temperature, and pH.

DETERMINANTS OF THE ARTERIOVENOUS PARTIAL PRESSURE OF CARBON DIOXIDE DIFFERENCE

As carbon dioxide is produced in the mitochondria as a byproduct of aerobic metabolism, and eliminated by the alveoli, there is a continuous concentration gradient of this gas from tissue to alveoli.

Mixed Venous Carbon Dioxide Tension

Normal mixed venous CO₂ tension (PvCO₂) is about 46 mmHg. This is the end result of admixture of blood draining from various tissues with different metabolic activity like skin with low metabolism and low-venous CO₂ and heart with a high. The PaCO₂ is identical to pulmonary end capillary CO₂ tension (PcCO₂).

Arterial Carbon Dioxide Tension

Arterial CO₂ tension, which is readily measurable, is identical to PcCO₂. Normal PaCO₂ is 38 ± 4 mmHg (5.1 ± 0.5 kPa); in practice, 40 mmHg is usually considered normal.

CARBON DIOXIDE PRODUCTION

There are two components to tissue CO₂ production: CO₂ produced in the mitochondria's tricarboxylic acid cycle as a result of oxidative phosphorylation (aerobic VCO₂) and CO₂ resulting from bicarbonate buffering of hydrogen ions produced by anaerobic sources of energy (anaerobic VCO₂). Total CO₂ production is the sum of these two.

$$VCO_2 = (VCO_2)_{\text{aerobic}} + (VCO_2)_{\text{anaerobic}}$$

Under aerobic conditions, hydrogen ions derived from the hydrolysis of adenosine triphosphate (ATP) are recycled during oxidative phosphorylation in the mitochondria.¹⁵

Aerobic Venous Carbon Dioxide Component

The relationship between venous oxygen (vO₂) and aerobic venous carbon dioxide (vCO₂) is defined by the cellular respiratory quotient (RQ):

$$RQ = VCO_2 / VO_2$$

Respiratory quotient depends on the type of substrate consumed, that is glucose, free fatty acids, or a combination thereof. It may vary between 0.7 and 1 with respect to the predominant energy source; for instance when lipids are the major fuel sources, R is close to 0.7 whereas under conditions of high-carbohydrate intake R approaches 1.¹⁵ Therefore, CO₂ production should augment either with increased oxidative metabolism or for a constant vO₂ when an equilibrated feeding regimen is replaced by a high-carbohydrate intake regimen. Under both conditions, CmvCO₂ - CaCO₂ difference or ΔpCO₂ should increase. Conversely, CO₂ production should decrease when oxidative metabolism is decreased either because of decrease in global oxygen demand or because of hypoxic conditions.

Anaerobic Venous Carbon Dioxide Component

Under hypoxic conditions of oxygen scarcity, the rate of cellular ATP production is the sum of mitochondrial and anaerobic ATP production. The latter is derived from glycolysis, the creatine kinase, and the adenylate kinase reactions. During dysoxia, however, the hydrolysis of ATP results in the generation of H⁺ that accumulates in the cytosol. H⁺ leaving the cell is weakly bound to lactate or buffered by bicarbonate in the interstitial fluid to produce CO₂.¹⁶

CARDIAC OUTPUT

The Fick principle relies on the observation that the total uptake of (or release of) a substance by the peripheral tissues is equal to the product of the blood flow to the peripheral tissues and the arteriovenous concentration difference (gradient) of the substance. In the determination of cardiac output, the substance most commonly measured is the oxygen content of blood thus giving the arteriovenous oxygen difference, and the flow calculated is the flow across the pulmonary system. This gives a simple way to calculate the cardiac output:

$$\text{Cardiac output} = \frac{\text{Oxygen consumption}}{\text{Arteriovenous oxygen difference}}$$

The Fick equation applied to CO_2 indicates that the CO_2 excretion (equivalent to CO_2 production in a steady state) equals the product of cardiac output by the difference between C_{CO_2} in mixed venous blood (C_{mvCO_2}) and in arterial blood (C_{aCO_2}):

$$v\text{CO}_2 = \text{cardiac output} \times (\text{C}_{\text{mvCO}_2} - \text{C}_{\text{aCO}_2})$$

The normal relationship between CO_2 pressure and content is almost linear over the usual physiological range of the CO_2 contents so that pCO_2 can be taken as a measure of C_{CO_2} .¹⁷ Thus, by substituting pCO_2 for C_{CO_2} and considering that $\Delta\text{pCO}_2 = k \times (\text{C}_{\text{mvCO}_2} - \text{C}_{\text{aCO}_2})$, a modified Fick equation can be obtained:

$$v\text{CO}_2 = \text{cardiac output} \times k \times \Delta\text{pCO}_2$$

Thus, $\Delta\text{pCO}_2 = k \times v\text{CO}_2 / \text{cardiac output}$, where k is assumed to be constant. Accordingly, ΔpCO_2 would be linearly related to CO_2 production and inversely related to cardiac output. Under aerobic steady-state conditions $v\text{CO}_2$ approximates $v\text{O}_2$ and, consequently, the mixed venous-to-arterial CO_2 content difference ($\text{C}_{\text{mv-aCO}_2}$) approximates the arterial to-mixed-venous O_2 content difference ($\text{C}_{\text{a-vO}_2}$). In other words, CO_2 production should not be higher than O_2 availability and, therefore, the $v\text{CO}_2/v\text{O}_2$ ratio (i.e., the RQ) should not be higher than 1.0. According to the modified Fick equation, ΔpCO_2 should be inversely correlated to cardiac output. The $\Delta\text{pCO}_2/\text{cardiac output}$ relationship depends on the level of $v\text{CO}_2$, so that a family of hyperbolic $\Delta\text{pCO}_2/\text{cardiac output}$ relationship curves for various levels of $v\text{CO}_2$ ($v\text{CO}_2$ isopleths) can be drawn (Fig. 2). Under conditions of stable $v\text{O}_2$ and $v\text{CO}_2$, ΔpCO_2 was observed to increase along with the decrease in cardiac output.¹⁸ Such an increase in ΔpCO_2 following cardiac output reduction is explained by the CO_2 stagnation phenomenon. Because of transit time slowing, a greater than normal addition of CO_2 per unit of blood crossing the efferent microvessels tends to generate hypercapnia in the venous blood. As long as pulmonary ventilation is adequate, a gradient will develop between P_{mvCO_2} and P_{aCO_2} . However, under spontaneous breathing conditions, hyperventilation, stimulated by the reduced blood flow, may decrease P_{aCO_2} and thus may prevent the CO_2 stagnation associated increase in P_{mvCO_2} . This finding underlines the usefulness of calculating ΔpCO_2 rather than simply measuring P_{mvCO_2} , in particular in the case of spontaneous breathing patient.¹⁹

It is noteworthy that the $\Delta\text{pCO}_2/\text{cardiac output}$ relationship is not linear but curvilinear such that a change of cardiac output will result in a greatest increase in ΔpCO_2 in the lowest range of cardiac output than in the highest range of cardiac output. In summary, during aerobic conditions, ΔpCO_2 is expected to be abnormally high (>6 mmHg), if cardiac output is low except in the case of low-metabolic demand.

In Hypoxic Condition

Carbon Dioxide Production

During circulatory shock, a global decrease in $v\text{O}_2$ should be accompanied by a reduction in aerobic CO_2 production. However, experimental models demonstrate that $v\text{CO}_2$ exhibits a slighter decrease than $v\text{O}_2$,^{20,21} thus pathologically increasing the $v\text{CO}_2/v\text{O}_2$ ratio as consequence of predominant anaerobic metabolism (Fig. 1). Interestingly, after shock reversion, the $v\text{CO}_2/v\text{O}_2$ ratio returns to normal values, suggesting the potential reversibility of this phenomenon, at least during the early stages of shock.

It has been postulated that tissue CO_2 concentration increases during dysoxia as hydrogen ions generated by anaerobic sources of energy are buffered by bicarbonate. Indeed, under anaerobic conditions, H^+ ions are generated by two mechanisms:¹⁹

1. Excessive production of lactic acid related to accelerated anaerobic glycolysis, since pyruvate can no longer be cleared by the Krebs cycle
2. Hydrolysis of ATP and of adenosine diphosphate. The generated protons will then be buffered by HCO_3^- ions, into the cell so that CO_2 will be generated.

The degree of significance of this so-called "anaerobic CO_2 production" is a matter of debate.²² In fact, the production of CO_2 from anaerobic pathway is difficult to detect since the efferent venous blood flow can be high enough to washout the CO_2 produced from the tissues. Moreover, because the marked fall of CO_2 production from aerobic pathway occurring under these circumstances, the total production of CO_2 should markedly decrease. Therefore, pCO_2 could not be augmented in the draining vein and the so-called "anaerobic

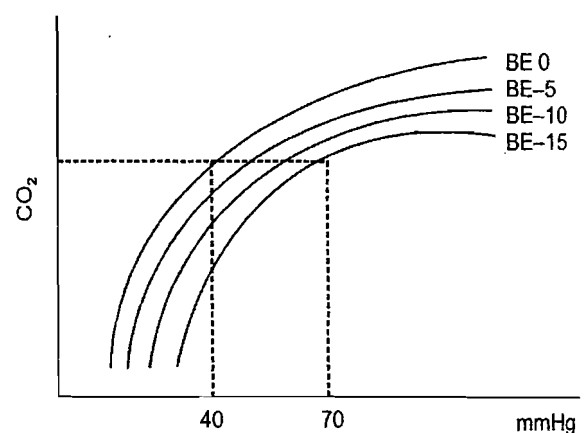


FIG. 1: Carbon dioxide (CO_2) pressure/ CO_2 content relationship and metabolic acidosis. When metabolic acidosis worsens [from base excess (BE) 0 to -15 mmol/L], the relationship is shifted to the right. Therefore, a given value of pulmonary capillary oxygen content could be associated either to a partial pressure of carbon dioxide (pCO_2) of 40 mmHg in normal conditions or to a pCO_2 of 70 mmHg for a severe metabolic acidosis (BE-15)

CO₂ production" could not be detected from the calculation of $\Delta p\text{CO}_2$.

However, in experimental models of myocardial ischemia induced by ventricular fibrillation or prolonged coronary artery occlusion, striking elevations of $p\text{CO}_2$ consistent with anaerobic CO₂ production were measured in the myocardium or in the cardiac vein.^{20,21}

On the other hand, in all experimental studies where $v\text{CO}_2$ was measured during hypoxia, $v\text{CO}_2$ was reported to decrease²³ suggesting that the decrease in CO₂ production due to reduced aerobic metabolism was predominant and that the anaerobic CO₂ production was of minor importance. Now, in two studies, $v\text{CO}_2$ decreased less than $v\text{O}_2$ suggesting that some anaerobic CO₂ generation had probably occurred.²³

K Factor

From the discussions above we know that:

$$k = \Delta p\text{CO}_2 / (\text{CmvCO}_2 - \text{CaCO}_2)$$

Or, $k = (\Delta p\text{CO}_2 \times \text{cardiac output}) / v\text{CO}_2$

As mentioned earlier, hematocrit, oxygen saturation, temperature, and pH influence the $p\text{CO}_2/\text{CcO}_2$ relationship, as such, k is not constant even in physiological conditions. In particular, metabolic acidosis results in a shift in the $p\text{CO}_2/\text{CcO}_2$ relationship such that for a given value of CcO_2 , $p\text{CO}_2$ is higher in the case of metabolic acidosis than in the case of normal pH (Fig. 1). During tissue hypoxia, " k " should increase owing to the presence of tissue metabolic acidosis. In an animal study, where tissue hypoxia was induced by cardiac tamponade, independent measurements of $\Delta p\text{CO}_2$, cardiac output, and $v\text{CO}_2$ allowed to estimate the k factor and its change with hypoxia. A striking rise (sixfold) of k was observed after induction of tissue hypoxia. Thus, during hypoxia, " k " should increase while $v\text{CO}_2$ should decrease. Obviously, the resultant effect on $\Delta p\text{CO}_2$ depends on the third determinant, the cardiac output.

Cardiac Output

It is important to distinguish two different situations: (i) tissue hypoxia with reduced cardiac output and (ii) tissue hypoxia with normal or high-cardiac output.

Tissue Hypoxia with Decreased Blood Flow

Experimental studies¹⁸ in which blood flow was reduced below the critical limit of supply dependency showed that $\Delta p\text{CO}_2$ could increase significantly when very low values of cardiac output are achieved. This fact can be explained by the three following reasons:

- An increase in venous $p\text{CO}_2$ secondary to low-flow-induced CO₂ stagnation^{24,25}

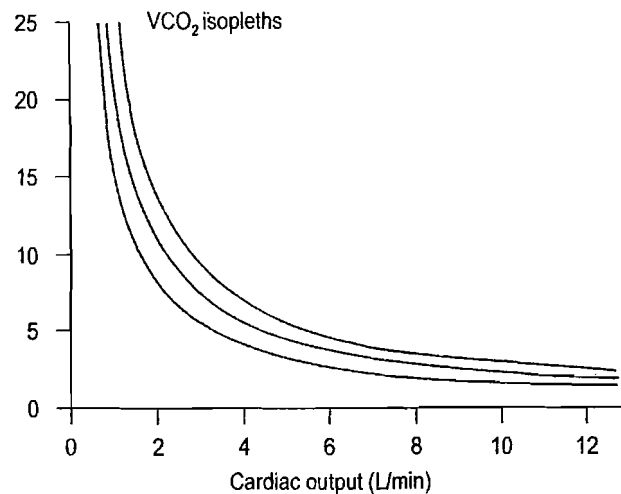


FIG. 2: Venous-to-arterial carbon dioxide partial pressure difference ($\Delta p\text{CO}_2$)/cardiac output relationships. According to the modified Fick equation, the $\Delta p\text{CO}_2$ /cardiac output relationship is curvilinear. Therefore, for a constant venous carbon dioxide ($v\text{CO}_2$), changes in cardiac output result in large changes in $\Delta p\text{CO}_2$ in the low values of cardiac output, whereas changes in cardiac output will not result in significant changes in $\Delta p\text{CO}_2$ in the high values of cardiac output. These relationships are further more complex when changes in cardiac output are accompanied by changes in $v\text{CO}_2$ and thereby by a transfer for one $v\text{CO}_2$ isopleth to another one (on the figure $v\text{CO}_2$ increases from the left to the right)

- An increase in RQ with persistent additional CO₂ production ($v\text{CO}_2$), relative to the O₂ uptake, secondary to the buffering of excess hydrogen ions by bicarbonate²⁶
- An increase in CO₂ production and stagnation although a ScvO_2 70%.

As the relation between cardiac output and $\text{CmvCO}_2 - \text{CaCO}_2$ difference is not linear but curvilinear (Fick equation) (Fig. 2), a dramatic increase in $\text{CmvCO}_2 - \text{CaCO}_2$ difference must be observed for a decrease in cardiac output in its lowest range. In fact, although this mathematical phenomenon may be strong under conditions of maintained $v\text{CO}_2$, it should be attenuated in hypoxic conditions since the decrease in $v\text{CO}_2$ rightward shifts the $v\text{CO}_2$ isopleth, which describes the $\text{CmvCO}_2 - \text{CaCO}_2$ difference/cardiac output relationship.

The striking widening of $\Delta p\text{CO}_2$ at very low-cardiac output may also be explained by the curvilinearity of the relationship between CmvCO_2 and PmvCO_2 in the highest range of CcO_2 so that changes in $\Delta p\text{CO}_2$ are greater than changes in $\text{CmvCO}_2 - \text{CaCO}_2$ difference in such extreme conditions (Fig. 1). Consequently, in the case of low-flow states, the increase in PmvCO_2 resulting from CO₂ stagnation is of greater extent than the increase in CmvCO_2 .

Tissue Hypoxia with Maintained Blood Flow

Under conditions of tissue hypoxia, the putative increase in anaerobic CO₂ production is over ridden by the decrease in aerobic CO₂ production.⁹ If the blood flow is maintained with

a normal or high-cardiac output then this less-produced CO_2 should be easily washed-out so that CmvCO_2 as well as the $\text{CmvCO}_2 - \text{CaCO}_2$ difference should not increase. Although the "k" factor should increase in these hypoxic conditions, PmvCO_2 and ΔPCO_2 should not increase. Vallet et al.²⁶ in their model of isolated dog hind limb showed that ΔPCO_2 significantly increased when limb hypoxia was induced by ischemia (low-blood flow) while it remained unchanged when hypoxia was related to hypoxemia (while blood flow was maintained). Similar results were observed in an *in vivo* conditions in pigs²⁴ and in sheep.²⁷ These studies underline that the absence of elevated ΔPCO_2 does not preclude the presence of tissue hypoxia and that a decreased blood flow is the major determinant in the increased ΔPCO_2 . Gutierrez²² in a mathematical model analysis and some clinical studies have also suggested that the reduced blood flow plays the key role in the widening of ΔPCO_2 observed under conditions of low-blood flow with tissue hypoxia.²⁸

Mecher et al.²⁸ found that the subgroup of septic shock patients with $\Delta\text{PCO}_2 > 6$ mmHg had a mean cardiac output significantly lower than the subgroup of those with $\Delta\text{PCO}_2 < 6$ mmHg. The two subgroups did not differ in terms of degree of hyperlactemia and of arterial hypotension. In other words, a number of patients of this study (18/37) had normal ΔPCO_2 despite patent tissue hypoxia, probably because their high-blood flow easily remove the CO_2 produced at the periphery. In the subgroup of patients with high ΔPCO_2 , volume resuscitation resulted in a decrease in ΔPCO_2 associated with an increase in cardiac output. The authors reasonably concluded that in patients with septic shock, an increased ΔPCO_2 is associated with a reduced systemic blood flow.

Bakker et al.¹⁸ also demonstrated that ΔPCO_2 was mostly related to cardiac output. In their study including 64 patients with septic shock, only 15 patients had a ΔPCO_2 higher than normal (> 6 mmHg). These patients had a lower cardiac output than the patients with normal ΔPCO_2 . Moreover, opposite changes in ΔPCO_2 and in cardiac output during the course of septic shock were observed. Interestingly, patients with a high ΔPCO_2 had similar vO_2 and blood lactate than those with a normal ΔPCO_2 . Although vCO_2 and vO_2 were not measured directly, these data suggest that differences in CO_2 production did not account for differences in ΔPCO_2 . Clearly, studies of Mecher et al.²⁸ and Bakker et al.¹⁸ underlined the poor sensitivity of ΔPCO_2 to detect tissue hypoxia, since ΔPCO_2 was normal in most patients with sepsis-related circulatory shock except with those with low-cardiac output. The major role of cardiac output in the widening of ΔPCO_2 was confirmed by the study of Wendon et al.²⁹ including hypotensive patients with fulminant hepatic failure. The major finding was that ΔPCO_2 was low (< 3 mmHg) despite evident tissue hypoxia. This was probably explained by a low production of CO_2 —as suggested by the low vO_2 (119 mL/min/m^2)—easily removed by the very high level of systemic blood flow ($\text{CI} = 5.4 \text{ L/min/m}^2$). These findings underline the fact that tissue

hypoxia under conditions of high-flow states should result in decreased (or normal) rather than increased ΔPCO_2 .

A $\text{ScvO}_2 > 70\%$ and a high ΔPCO_2 in septic patient was associated with a low CI, which is an indicator of microcirculatory impairment. In study by Valle et al., underresuscitated patients could be identified by a high ΔPCO_2 even if they have an adequate ScvO_2 as per the current guidelines. This finding was also substantiated in a study by Bakker et al.¹⁰ where high ΔPCO_2 was associated with poor outcome and higher lactate levels in patients with sepsis. A high ΔPCO_2 can occur due to various reasons. ΔPCO_2 is related linearly to CO_2 production and inversely to cardiac output.¹⁰ Uneven distribution of microcirculatory flow leads to increase of venous blood carbon dioxide.²⁹⁻³¹ This may lead to increase of ΔPCO_2 because of a decreased washout.³² ΔPCO_2 can become an important marker of tissue hypoperfusion.^{30,33} Two mechanism of increased ΔPCO_2 in shock state has been described by Durkin et al. At first, lower blood flow in shock patients leads to a longer blood transit time in the microcirculation causing more carbon dioxide to diffuse into the venous blood. Secondly, due to increased minute ventilation and ventilation/perfusion mismatch, arterial partial pressure of carbon dioxide decreases.²⁸ Increase in anaerobic metabolism leading to increased carbon dioxide production may also lead to increased ΔPCO_2 .^{28,34}

CLINICAL USE OF VENOUS-TO-ARTERIAL CARBON DIOXIDE DIFFERENCE

Interpretation of Venous-to-arterial Carbon Dioxide Difference in Shock States

Venous-to-arterial carbon dioxide difference can be calculated after simultaneous sampling of arterial blood (PaCO_2) and of mixed venous blood from the distal end of a pulmonary artery catheter (PmvCO_2). Under physiological conditions, ΔPCO_2 ranges from 2 to 5 mmHg.

The clinical implications of this concept can be summarized as follows:

- An increased ΔPCO_2 may suggest that cardiac output is not high enough with respect to the global metabolic conditions
- Under suspected hypoxic conditions (for instance with increased blood lactates), the presence of a high ΔPCO_2 could be one of the arguments that would incite the clinician to increase cardiac output in the attempt to reduce tissue hypoxia
- Under aerobic conditions, the presence of a high ΔPCO_2 would mean that blood flow is not high enough, even if cardiac output is in the normal range. This condition can be associated with an increased oxygen demand and hence increased CO_2 production. However, whether further increasing cardiac output can prevent short-term subsequent risks of onset of tissue hypoxia actually remains to be proved

- In a patient with a high-initial value of $\Delta p\text{CO}_2$, following the time-course of $\Delta p\text{CO}_2$ can also be helpful to assess the global metabolic effects of a therapeutic intervention aiming at increasing cardiac output. Under conditions of oxygen supply-dependence, an increase in cardiac output must be accompanied by increases in $v\text{O}_2$ and in $v\text{CO}_2$ so that $\Delta p\text{CO}_2$ is expected to decrease by a lesser extent than in the case of oxygen supply independence. Consequently, relatively unchanged $\Delta p\text{CO}_2$ with therapy would not mean that the therapy has failed. In this case, the therapeutic agent would be rather maintained and its dose even increased until obtaining a frank decrease in $\Delta p\text{CO}_2$ that would indicate that the critical level of oxygen delivery has been actually overpassed
- Venous-to-arterial carbon dioxide difference can also be helpful to choose the appropriate dose of a therapeutic agent known to have thermogenic effects. For instance, catecholamines by their β -adrenergic stimulation may exert thermogenic effects and are, therefore, able to increase both $v\text{O}_2$ and $v\text{CO}_2$.²² Accordingly, $\Delta p\text{CO}_2$ —as an index of the $v\text{CO}_2$ /cardiac output ratio—was shown to detect changes in oxygen demand accompanying dobutamine-induced changes in cardiac output.³² In this regard, $\Delta p\text{CO}_2$ together with mixed venous oxygen saturation (SvO_2)³³ may help to titrate drug therapy.
- It must be kept in mind that a normal $\Delta p\text{CO}_2$ does not preclude inadequacy of blood flow with metabolic condition at a regional level, for instance in the splanchnic area, as demonstrated in an experimental study.³⁵ In septic shock patients with high-cardiac output (and hence presumably low $\Delta p\text{CO}_2$), inadequate splanchnic blood flow or increased difference between gastric mucosal and arterial $p\text{CO}_2$ ³⁶ were reported. This point is of importance because gut mucosal ischemia could play a pivotal role in the development of multiple organ failure³⁷
- There are numerous potential causes of errors of $p\text{CO}_2$ measurements: incorrect sample container, inadequate sample volume relative to anticoagulant volume, contaminated sample by air or venous blood or catheter fluid, improper transport conditions, length of the delay between acquisition and analysis, etc. Although all these potential errors may be prevented, there is still a proper instrument imprecision of ± 1 mmHg, even with the most recent models of blood gas analyzers.³⁸ This range of error is relatively high as compared to the normal range of $\Delta p\text{CO}_2$. Therefore, clinicians must be very careful in the interpretation of low values of $\Delta p\text{CO}_2$ and of small changes in $\Delta p\text{CO}_2$.

LIMITATIONS IN THE INTERPRETATION OF VENOUS-TO-ARTERIAL CARBON DIOXIDE DIFFERENCE

- Calculating $v\text{CO}_2$ by multiplying Cmv-aCO_2 with blood flow is only valid under steady-state conditions. If poorly perfused tissues regain flow, CO_2 stores are washed-out and calculated CO_2 production is likely to be overestimated
- The amount of anaerobically produced CO_2 is low compared to CO_2 produced under aerobic conditions. It is therefore be questioned whether such small amounts can increase the $v\text{CO}_2$ above $v\text{O}_2$. For instance, when O_2 delivery (DO_2) was stepwise reduced to 16% of baseline values in an *in situ*, vascularly isolated, innervated dog limb, $v\text{O}_2$ remained above $v\text{CO}_2$ despite continually increasing RQ.²⁶ Admittedly, the hind limb $v\text{CO}_2/v\text{O}_2$ relationship may not represent global RQ well
- When blood flow is high, large changes in cardiac output will not result in significant changes in $\Delta p\text{CO}_2$, because of the curvilinearity of the relationship between CO_2 differences and cardiac output (Fig. 2). This point was illustrated in a series of patients with high-systemic blood flow but without evidence of tissue hypoxia and in whom significant changes in cardiac output were associated with unchanged $\Delta p\text{CO}_2$ values. Accordingly, interpretation of $\Delta p\text{CO}_2$ changes (or of absence of $\Delta p\text{CO}_2$ changes) must be particularly cautious under conditions of very high-systemic blood flow

COMBINED ANALYSIS OF VENOUS-TO-ARTERIAL CARBON DIOXIDE DIFFERENCE AND OXYGEN-DERIVED PARAMETERS

In shock states, aerobically generated CO_2 decreases together with O_2 consumption ($v\text{O}_2$). When $v\text{O}_2$ becomes dependent on DO_2 , CO_2 can be produced anaerobically mostly due to bicarbonate buffering of protons produced in excess secondary to the hydrolysis of ATP, so that $v\text{CO}_2$ can exceed $v\text{O}_2$. It has been estimated that anaerobic ATP compensates approximately 6% of the accumulated O_2 debt.²² Therefore, an RQ more than one may be interpreted as a sign of anaerobic metabolism, since it may indicate that more CO_2 is produced than O_2 is consumed (Fig. 3), although both are decreased. According to the Fick equation, $v\text{CO}_2$ equals the product of cardiac output by the difference between mixed venous and arterial CO_2 contents (Cmv-aCO_2) whereas $v\text{O}_2$ equals the product of cardiac output by the difference between arterial and mixed $v\text{O}_2$ contents (Ca-mvO_2) (Fig. 3). By eliminating the cardiac output value, which is common to the numerator and denominator of the RQ (Fig. 3) and taking $p\text{CO}_2$ as a surrogate of CO_2 content, an increased ratio between mixed venous-arterial $p\text{CO}_2$ difference and Cmv-aCO_2 ($\text{Pmv-aCO}_2/\text{Ca-mvO}_2$) was shown to be a good indicator of anaerobiosis assessed by hyperlactemia.³⁹ However, the relationship between CO_2 content and $p\text{CO}_2$ is curvilinear rather than linear and is influenced by the degree of metabolic acidosis, the hematocrit and the O_2 saturation. Ospina-Tascon et al.⁴⁰ demonstrated that a $\text{Cmv-aCO}_2/\text{Ca-mvO}_2$ more than one predicts outcome early in septic shock, similar to increased arterial lactate concentration. Patients with both

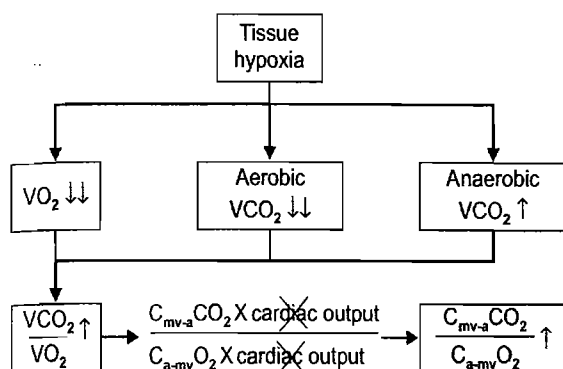


FIG. 3: In cases of shock states, tissue hypoxia results in decreased oxygen consumption (VO_2) and aerobically generated carbon dioxide (CO_2) production (VCO_2). However, the global vCO_2 decreased to a lesser extent than VO_2 due to production of anaerobically generated CO_2 . Consequently, the vCO_2 over VO_2 ratio increases. Therefore, after elimination of cardiac output (present in both numerator and denominator), the difference between mixed venous and arterial CO_2 contents ($\text{C}_{\text{mv-aCO}_2}$) over the difference between arterial and mixed VO_2 contents ($\text{C}_{\text{a-mvO}_2}$) should increase in such hypoxic conditions

an increased $\text{C}_{\text{mv-aCO}_2}/\text{C}_{\text{a-mvO}_2}$ and lactate concentration 6 hours after the study start had the highest mortality.⁴⁰ The authors propose that the $\text{C}_{\text{mv-aCO}_2}/\text{C}_{\text{a-mvO}_2}$ could become a resuscitation target.⁴⁰

CENTRAL VENOARTERIAL CARBON DIOXIDE DIFFERENCE

The mixed venoarterial pCO_2 difference is determined by subtracting the peripheral arterial pCO_2 from the mixed venous pCO_2 [pulmonary artery (PA)]. Obtaining a mixed venoarterial (v-a) pCO_2 difference requires access to the PA circulation and thus has limitations similar to the pulmonary artery catheterization (PAC). Furthermore, if a PAC is in place, cardiac output can be obtained by thermodilution, and the clinical utility of an alternative method of measurement is diminished. In contrast, central venous (CV) access is more frequently and easily obtained, yet no direct measure of cardiac output can be calculated. The substitution of a CVpCO_2 for a mixed venous pCO_2 may yield a similar inverse relationship to cardiac output.⁴¹ Cuschieri J, et al.⁴² in their prospective cohort study on 83 critically ill patients had found that substitution of a central for a mixed venoarterial pCO_2 difference provides an accurate alternative method for calculation of cardiac output.

CONCLUSION

While resuscitating patients with septic shock, ΔpCO_2 can be considered as a standard marker for the adequacy of cardiac output. Raised ΔpCO_2 can be a strong indicator for raising cardiac output, however, in the early stage of septic shock, when the patients have hyperdynamic circulation, ΔpCO_2 may not be high due to rapid clearance of CO_2 from

circulation. In such hyperdynamic conditions interpretation of ΔpCO_2 should be done with caution.

REFERENCES

- Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med.* 2014;40:1795-815.
- Rivers E, Nguyen B, Ressler J, et al. Group EG-DTC Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-77.
- Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest.* 2006;129:225-32.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med.* 2012;39:165-228.
- Bellomo R, Reade MC, Warrillow SJ. The pursuit of a high central venous oxygen saturation in sepsis: growing concerns. *Crit Care.* 2008;12:130.
- Perel A. Bench-to-bedside review: the initial hemodynamic resuscitation of the septic patient according to Surviving Sepsis Campaign guidelines—does one size fit all? *Crit Care.* 2008;12:223.
- Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370:1683-93.
- Textoris J, Fouché L, Wiramus S, Antonini F, et al. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. *Crit Care.* 2011;15:R176.
- Dong G, Liu C, Xu B, et al. Postoperative abdominal complications after cardiopulmonary bypass. *J Cardiothorac Surg.* 2012;7:108.
- Bakker J, Vincent J, Gris P, et al. Veno-arterial carbon dioxide gradient in human septic shock. *Chest.* 1992;101:509-515.
- Vallée F, Vallet B, Mathe O, Parraguet J, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med.* 2008;34:2218-25.
- Futier E, Robin E, Jabaudon M, et al. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care.* 2010;14:R193.
- Silva JM, Oliveira AMRR, Segura JL, et al. A large venous-arterial pCO_2 is associated with poor outcomes in surgical patients. *Anesthes Res Pract.* 2011;2011:759792.
- Hernandez G, Regueira T, Bruhn A, et al. Relationship of systemic, hepato-splanchnic, and microcirculatory perfusion parameters with 6-hour lactate clearance in hyperdynamic septic shock patients: an acute, clinical physiological, pilot study. *Ann Intensive Care.* 2012;2:1-9.
- West JB. Gas transport to the periphery: how gases are moved to the peripheral tissues? In: West JB (Eds). *Respiratory Physiology. The essentials*, 4th ed. Baltimore: Williams & Wilkins; 1990. Pp. 69-85.
- Connett RJ, Honig CR, Gayeski TEJ, et al. Defining hypoxia: a systems view of vO_2 , glycolysis, energetics, and intracellular pO_2 . *J Appl Physiol.* 1990;68:833-42.
- Groeneveld ABJ. Interpreting the venous-arterial pCO_2 difference. *Crit Care Med.* 1998;26:979-80.
- Van der Linden P, Rausin I, Bekrar Y, et al. Detection of tissue hypoxia by arteriovenous gradient for PCO_2 and pH in anesthetized dogs during progressive hemorrhage. *Anesth Analg.* 1995;80:269-75.
- Benjamin E. Venous hypercarbia: a nonspecific marker of hypoperfusion. *Crit Care Med.* 1994;22:9-10.
- Von Planta M, Weil MH, Gazmuri RJ, et al. Myocardial acidosis associated with CO_2 production during cardiac arrest and resuscitation. *Circulation.* 1989;80:684-92.
- Kette F, Weil MH, Bisera J, et al. Intramyocardial hypercarbic acidosis during cardiac arrest and resuscitation. *Crit Care Med.* 1993;21:901.
- Gutierrez G. A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. *Am J Respir Crit Care Med.* 2004;169:525-33.

23. Cohen IL, Sheikh FM, Feustel PJ, et al. Effect of hemorrhagic shock and reperfusion on the respiratory quotient in swine. *Crit Care Med*. 1995;23:545-52.
24. Nevriere R, Chagnon JL, Vallet B, et al. Small intestine intramucosal PCO₂ and microvascular blood flow during hypoxic and ischemic hypoxia. *Crit Care Med*. 2002;30:379-84.
25. Gutierrez G, Wulf ME. Lactic acidosis in sepsis: a commentary. *Intensive Care Med*. 1996;22:6-16.
26. Vallet B, Teboul JL, Cain S, et al. Venoarterial CO₂ difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol*. 2000;89:1317-21.
27. Dubin A, Murias G, Canales H, et al. Intramucosal-arterial PCO₂ gap fails to reflect intestinal dysoxia in hypoxic hypoxia. *Crit Care*. 2002;6:514-20.
28. Mecher CE, Rackow EC, Astiz ME, et al. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. *Crit Care Med*. 1990;18:585-9.
29. Wendon JA, Harrison PM, Keays R, et al. Arterial-venous pH differences and tissue hypoxia in patients with fulminant hepatic failure. *Crit Care Med*. 1991;19:1362-4.
30. Johnson BA, Weill MH. Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses. *Crit Care Med*. 1991;19:1432-8.
31. Chiolerio R, Flatt JP, Revelly JP, et al. Effects of catecholamines on oxygen consumption and oxygen delivery in critically ill patients. *Chest*. 1991;100:1676-84.
32. Teboul JL, Mercat A, Lenique F, et al. Value of venous-arterial PCO₂ gradient to reflect the O₂ supply to demand in humans. *Crit Care Med*. 1998;26:1007-10.
33. Teboul JL, Graini L, Boujdaria R, et al. Cardiac index vs oxygen-derived parameters for rational use of dobutamine in patients with congestive heart failure. *Chest*. 1993;103:81-5.
34. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO₂ collaborative group. *N Engl J Med*. 1995;333:1025-32.
35. Heino A, Haettkainen J, Merasto ME, et al. Systemic and regional PCO₂ gradients as markers of intestinal ischemia. *Intensive Care Med*. 1998;24:599-604.
36. Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism and gastric tonometric variables in septic shock. A prospective, randomized study. *Intensive Care Med*. 1997;23:282-7.
37. Fiddian-Green RG. Associations between intramucosal acidosis in the gut and organ failure. *Crit Care Med*. 1993;21:S103-5.
38. Crapo RO. Arterial blood gases: quality assessment. In: Tobin M (Eds). *Principle and practice of Intensive Care monitoring*. New-York: Mc Graw-Hill; 1998. Pp. 107-22.
39. Mekontso-Dessap A, Mekontso-Dessap A. Combination of venoarterial PCO₂ difference with arteriovenous O₂ content difference to detect anaerobic metabolism in patients. *Intensive Care Med*. 2002;28:272-7.
40. Ospina-Tasco'n GA, Uman'a M, et al. Combination of arterial lactate levels and venous-arterial CO₂ to arterial-venous O₂ content difference ratio as markers of resuscitation in patients with septic shock. *Intensive Care Med*. 2015;41:796-805.
41. Cuschieri J, Hays G, Rivers EP. Arterial-venous carbon dioxide gradients as an indicator of cardiac index: A comparison between the mixed and central circulation. *Crit Care Med*. 1998;26:A56.
42. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med*. 2005;31:818-22.

Heart-lung Interactions

Suresh Ramasubban

INTRODUCTION

The mechanics of heart and lung are both driven by pressure and these two organs share space in the thoracic cavity, so it is obvious that they will interact. This interaction is continuous, nonstop and occurs with every breath. The visceral pleura encase both the lungs and the parietal pleura lines the surface of the chest wall, mediastinum, heart, vena cava, and the aorta. Thus, all the structures are exposed to the pleural pressures (P_{pls}). Hence, the pressure changes in the pleura with respiration will affect the mechanical performance of the heart. The interactions depend on the nature of ventilation, spontaneous or positive pressure, as the intrathoracic variations have a phase change with type of ventilation. Heart-lung interactions are defined as the effects of spontaneous and mechanical ventilation on the circulation. Stephen Hales first documented these cardiopulmonary interactions in 1733, when he showed that blood pressure (BP) of healthy people fell during spontaneous inspiration. Heart-lung interactions are, therefore, responsible for cardiopulmonary homeostasis. During critical illness, these interactions are exaggerated either due to respiratory diseases or circulatory dysfunction.

To understand these interactions one needs to review the mechanics of ventilation and the functioning of the heart, to one effect, i.e., generation of cardiac output (CO). Initially, we will look at heart-lung interactions in a spontaneously breathing situation followed by mechanical ventilation. Subsequently, relevant clinical scenarios where these interactions play an important role will be discussed.

VENTILATION

Ventilation, which is defined as the bulk flow of gas from the atmosphere or ventilator into the lungs, has a distinct mechanics. For the bulk flow of gas to occur into and out of the lungs, the respiratory system expands above and then returns to its resting or equilibrium volume. There are two forces,

which oppose this movement of the respiratory system and pressure is required to overcome these two forces. These two forces are the elastic recoil of the lungs and the viscous forces of the respiratory system. The negative pressure changes in the pleura cause spontaneous inspiration with delivery of volume into the lungs. Expiration is a passive process with return of pressures to their baseline values. Mechanical ventilation has a phase shift with increased P_{pls} generating tidal volumes during inspiration.

Cardiac Output

Cardiac output is equal to stroke volume (SV) times the heart rate (HR).

$$CO = SV \times HR$$

Stroke volume is the amount of blood pumped out by the right and left ventricle (LV) in each beat. Stroke volume depends on preload, afterload, and contractility.

Preload

Theoretically, the length of the cardiac muscle fiber prior to contraction is the preload. Since, we cannot measure the load, we indirectly use the volume of blood in the ventricle prior to contraction as the preload, i.e., right- and left end-diastolic volume (RVEDV and LVEDV). According to Starling's law, the force of contraction increases with LVEDV up till a particular point (Fig. 1).

The preload is determined by three factors:

1. The volume of blood received in the right and left atrium
2. The time for ventricular filling, i.e. diastolic time
3. Compliance of the ventricles (diastolic dysfunction).

Afterload

This is the pressure generated by the LV and right ventricle (RV) to eject blood into the systemic and pulmonary circulation, respectively. The pulmonary circulation being

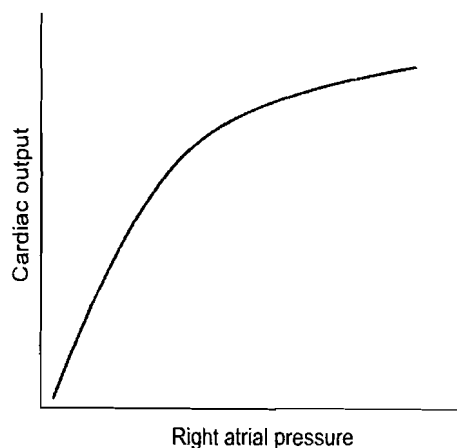


FIG. 1: Cardiac function curve: According to Starling's theory, the force of contraction and the cardiac output increases as the preload increases up to a certain point, where increase in right atrial pressure will not result in any further increase in cardiac output

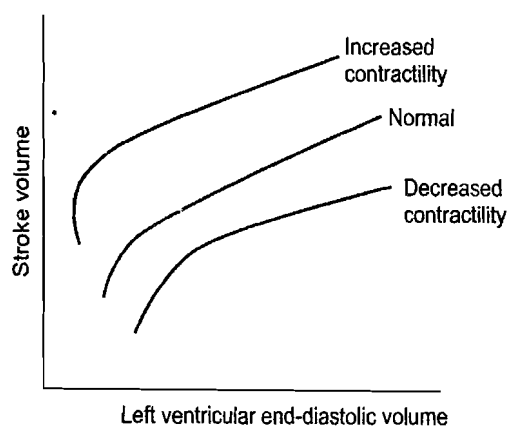


FIG. 2: A series of cardiac function curves. These curves show the different response as contractility changes on the stroke volume with change in left ventricular end-diastolic volume

a low-pressure circuit, the RV afterload is much lower as compared to the LV afterload.

Contractility

The native ability of the heart to generate pressure during systole refers to the contractile ability of the heart and any disease that damages the myocardium reduces it. The Starling curves of the heart changes with differences in contractility as shown in figure 2.

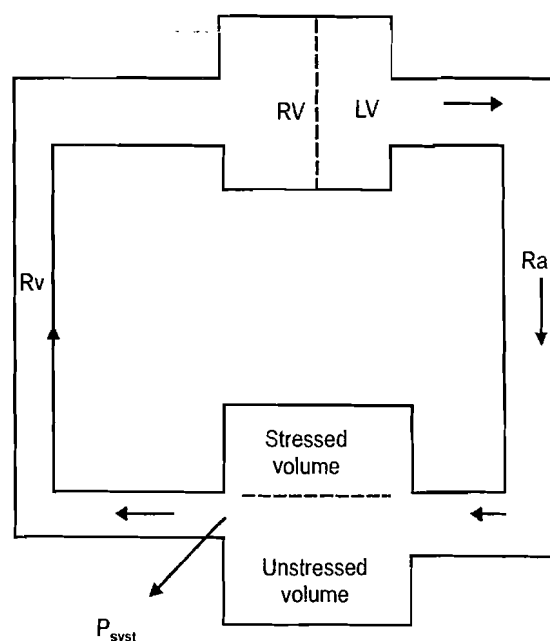
SYSTEMIC AND PULMONARY CIRCULATIONS

To understand the flow of blood in the systemic and pulmonary circulations, it is important to understand the circulatory system from a Guytonian physiology¹⁻³ rather than from only a Starling physiology,⁴ as described above. The

influence of the respiratory system on the circulatory system is much clearer to understand based on a combination of both these systems.

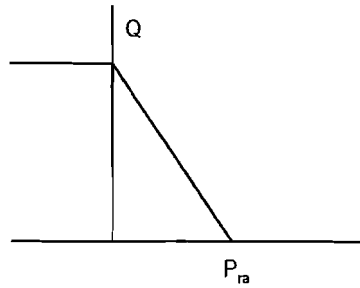
A simplified mechanical model of the systemic circulation as described by Fessler and depicted in figure 3 is used to explain the systemic circulation.⁵ The heart pumps blood into the arteries, which acts as a resistance, the blood then enters the capillaries and veins, lumped as reservoir with compliance, blood is then returned to the right atrium. The pressure at the outflow end of this venous reservoir is called mean systemic pressure (P_{syst}) or mean circulatory filling pressure (MCFP). The compliance of the systemic vessels and the volume of blood they contain determine P_{syst} . This pressure is the average of the pressures throughout the systemic circulation with contribution of each vascular segment weighted by its fraction of the total compliance of the systemic circulation. Since most of the compliance resides in the low-pressure veins, P_{syst} is closer to central venous pressure (CVP) than to arterial pressure. Guyton determined the MCFP by stopping the circulation and using a pump to rapidly equilibrate the arterial and venous pressure.

Blood flow to the reservoir thus requires the heart to contract, venous return occurs due to the small pressure gradient between MCFP and right atrial pressure (P_{ra}). Cardiac output is thus determined not only by the function of the heart [cardiac response curve, (Fig. 1)] but also the



RV, right ventricle; LV, left ventricle; Ra, arterial resistance; Rv, venous resistance; P_{syst} , mean systemic pressure.

FIG. 3: Simple model of the systemic circulation. The heart pumps blood through an arterial resistance into a reservoir. Pressure at the outlet of the reservoir is called mean systemic pressure, determined by the stressed volume and the compliance of the chamber. Total volume of the reservoir is the sum of stressed volume and unstressed volume. Venous return occurs passively, driven through the venous resistance by the pressure difference between mean systemic pressure and the right atrium



P_{ra} , right arterial pressure.

FIG. 4: Venous return curve. Venous return depends on the pressure difference between the mean circulatory filling pressure and right atrial pressure. As right arterial pressure falls, the venous return increases up till a point where P_{ra} becomes subatmospheric

function of the circuit [venous return curves, (Fig. 4)]. Thus, to predict the effect of respiration on the CO one needs to take into consideration both the ability of the heart to pump blood and also the tendency for blood to return to the heart from the blood vessels.

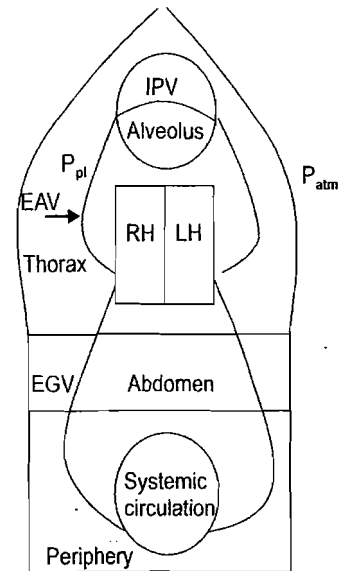
The pulmonary circulation is functionally similar to the systemic circulation. The RV pumps blood into the pulmonary reservoir, from which blood drains passively through a venous resistance into the left atrium.

Both the pulmonary and systemic venous resistance is very low and the entire CO is returned to the atriums by a very small pressure gradient of 5–10 mmHg.

A slightly more complicated model of the circulation (Fig. 5) as described by Fessler is essential to understand heart-lung interactions. In this model, the heart and lungs are surrounded by P_{pl} and the pulmonary circulation is divided into alveolar vessels (surrounded by alveolar pressure) and extra-alveolar vessels (surrounded by P_{pls}), which varies throughout the respiratory cycle. Intra-abdominal pressure increases with the diaphragm moving down during inspiration and comes back to baseline during expiration. The pressure in the periphery is unaffected by respiration and remains atmospheric throughout the respiratory cycle. Venous return to the right side of the heart is determined by the pressure gradient between the extrathoracic great veins and the right atrium and so will be affected by phase of respiration and type of ventilation.

PLEURAL PRESSURE AND THE CIRCULATORY SYSTEM^{6,7}

The mechanics of breathing impose some stresses on the surface of the heart, on the intrapulmonary vessels, on the ventricles due to expansion of the other ventricle, and on the abdominal vessels. The stresses on the surface of the heart and intrapulmonary vessels will be discussed here as these determine the heart-lung interactions.

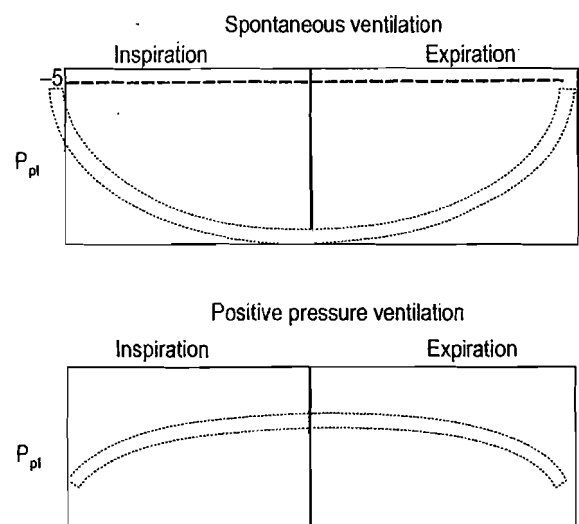


IPV, intrapulmonary valve; P_{atm} , atmospheric pressure; P_{pl} , pleural pressure; EAV, extra-alveolar vessels; EGV, extrathoracic great veins.

FIG. 5: Circulatory system model showing factors that affect venous return to the heart. Pleural pressures affect the heart and the extra-alveolar vessels. Peripheral circulation is unaffected by pleural pressures. Venous return depends on the pressure difference between the extrathoracic great veins and the right atrium

Effect of Pleural Pressure on the Surface of the Heart

Spontaneous inspiration leads to a decrease in P_{pl} , while expiration leads to an increase in P_{pls} while the changes are opposite during positive pressure ventilation (PPV) (Fig. 6).



P_{pl} , pleural effusion.

FIG. 6: Schematic representation of pleural pressure (P_{pl}) with respiration. The top panel shows P_{pl} decreasing during inspiration and increasing to baseline during spontaneous ventilation. The bottom panel shows the reverse with increase in P_{pl} with inspiration and decreasing to baseline during expiration

Let us look at the effect of P_{pl} changes on the right heart and left heart individually. The effects on the filling and emptying of the right side and left side will be analyzed separately.

Effect of Pleural Pressure on Right Heart Filling

An increase in the P_{pl} will increase the pressure on the surface of the right heart and in turn will elevate P_{ra} . Since P_{ra} is the downstream pressure for venous return, the increase in P_{ra} will decrease venous return to the right side of the heart. Since, the entire pressure gradient for venous return is only 5 mmHg, increase of P_{ra} by this much would be fatal, if not for compensatory mechanisms. These mechanisms include activation of the sympathetic reflexes, fluid, and sodium retention that will elevate MCFP and diminish the fall in venous return.

A decrease in P_{pl} (spontaneous inspiration or expiration on PPV) will decrease P_{ra} , which will increase venous return up till a maximum wherein P_{ra} becomes subatmospheric. Thus, there is a venous flow limitation and exaggerated inspiratory efforts will not augment venous return.

Effect of Pleural Pressure on Left Heart Filling

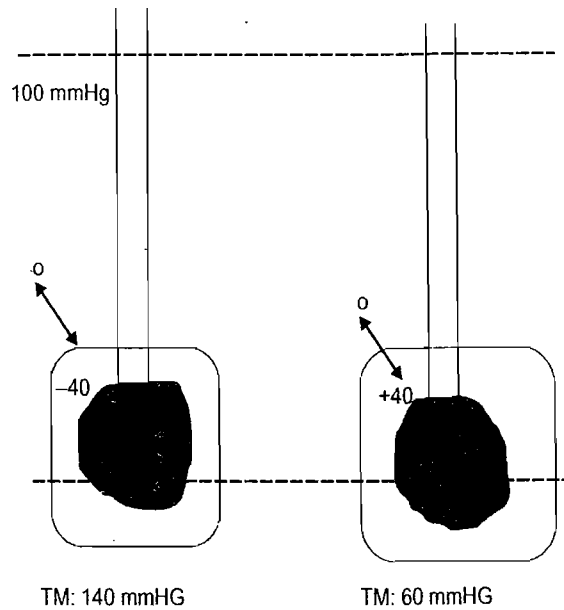
If lung volumes remain constant, the change in P_{pl} is felt equally by the pulmonary vessels and the LV. As a consequence, there is no effect on the pressure gradient determining LV filling.

Effect of Pleural Pressure on Left Heart Emptying

Left ventricular afterload, which is defined as the pressure that the LV needs to generate to eject blood, is directly proportional to the transmural LV pressure. Normally, the pressure outside the heart is near zero, it can be ignored. However, during disease states or PPV, P_{pl} can vary far from zero. As P_{pl} falls at constant arterial pressure, the heart must work harder to eject the blood. On the contrary, increase in P_{pl} will make it easier for the LV to pump as the transmural pressure falls with a positive P_{pl} . This is illustrated by the schematic in figure 7.

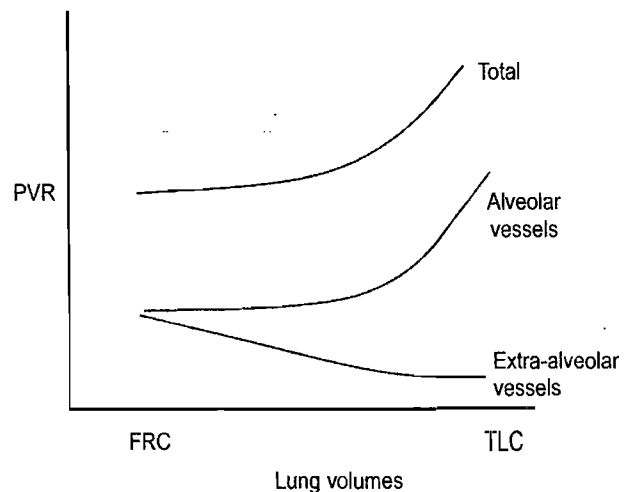
EFFECT OF RESPIRATION ON INTRAPULMONARY VESSELS

Pleural pressure changes do not have any effect on the pulmonary vessels as both alveolar and P_{pls} change equally. However, lung inflation and the consequent volume changes of the lung affect the intrapulmonary vessels. As shown in figure 5, due to the differing pressures on their surface, intra-alveolar and extra-alveolar vessels differ in their response to changes in lung volume. Extra-alveolar vessels enlarge with increasing lung volumes, decreasing their resistance



TM, transmural pressure.

FIG. 7: Schematic showing difference in transmural pressure (TM) with ventilation. Positive pressure ventilation decreases the TM across the left ventricle thereby decreasing left ventricle afterload with positive pressure ventilation



PVR, pulmonary vascular resistance; FRC, functional residual capacity; TLC, total lung capacity.

FIG. 8: Relationship between pulmonary vascular resistance (PVR) and lung volumes. Extra-alveolar vessels dilate with increasing lung volumes and alveolar vessels constrict and the net effect on PVR is an increase with increased lung volumes

and increasing their capacitance. Intra-alveolar vessels are compressed with increasing lung volumes, the resultant effect depends on their position in the lungs, i.e., corresponding to lung west zones (Fig. 8). The combined effect of all the zones is a biphasic response of pulmonary vascular resistance (PVR) to lung inflation. At lung volumes below the functional residual capacity (FRC), inflation will decrease PVR and above FRC, PVR will increase with inflation up till total lung capacity (TLC).

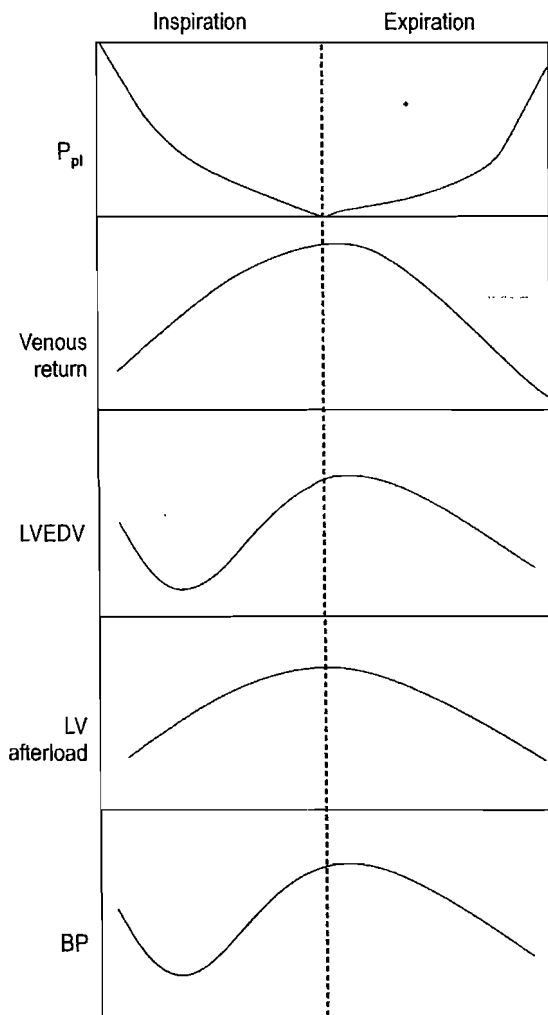
HEART-LUNG INTERACTIONS

The overall effect of spontaneous ventilation is to increase LV SV and CO, mostly through augmentation of venous return. Because of the transient fall in LV filling and SV, a small drop in BP normally occurs early in inspiration. Later in inspiration and expiration, the BP rises with increased LV preload and a drop in LV afterload (Fig. 9).

Since the breaths on a ventilator are in opposite phase to that of spontaneous ventilation, the effects on CO and BP are reversed, so BP normally rises early in inspiration then falls before returning to its baseline level.

CLINICAL APPLICATIONS⁸

The heart-lung interactions described above lead to either a transient effect or a steady state effect. Transient effects occur due to mechanical changes through a respiratory cycle



BP, blood pressure; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; P_{pl} , pleural pressure.

FIG. 9: Schematic showing hemodynamic changes during spontaneous ventilation. Pleural pressure decreases during inspiration, venous return increase to the right side, left ventricular end-diastolic volume falls, left ventricular afterload increases with a resultant fall in blood pressure initially during inspiration, and rise during expiration

or due to the effects of a respiratory maneuver. Steady state effects produce changes in CO or its distribution due to both mechanical and compensatory mechanisms.

Transient Effects

Pulsus Paradoxus

The exaggerated fall in inspiratory pressures due to inspiration is pulsus paradoxus. It is associated with pericardial tamponade, severe asthma, and hypovolemia. The detection of hypovolemia using this phenomenon forms the basis for modern hemodynamic monitoring in critical care.

Kussmaul's Sign

The inspiratory increase in P_{ra} (reflected in the jugular venous pressure) is Kussmaul's sign. It is seen with constrictive pericarditis classically and in the critical care unit this is used to identify RV failure due to infarction or pulmonary embolism.

Steady State Effects

Positive End-expiratory Pressure

Positive end-expiratory pressure (PEEP) generally decreases CO and the cause of this decrease is mostly related to the increase in P_{ra} , which decreases venous return.

Continuous Positive Airway Pressure

Increased CO or LV ejection fraction is reported when spontaneously breathing patient with congestive heart failure is placed on continuous positive airway pressure (CPAP). In acute cardiogenic pulmonary edema, use of CPAP instantaneously reduces preload and afterload, preventing intubations.

Weaning from Mechanical Ventilation

Change from a positive-pressure breath to a negative-pressure breath during weaning results in changes in mean P_{pl} , leading to increase in the venous return gradient and increase in LV afterload. Thus, weaning can be a cardiovascular challenge, especially for the failing heart and measures to relieve these stresses need to be undertaken to ensure successful weaning.

CONCLUSION

The heart and the lung share a common accommodation, i.e., the thorax and hence are linked to each other and thus the heart-lung interactions are inevitable. These effects are exaggerated in disease and can be a useful clinical monitoring tool. Interventions like mechanical ventilation and PEEP are

additional situations wherein the heart-lung interactions become important. The use of the heart-lung interactions in a mechanically ventilated patient has laid the foundation for modern hemodynamic monitoring. A systematic and physiological understanding of these interactions is necessary for the practice of critical care medicine.

REFERENCES

1. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev.* 1955;35:123-9.
2. Guyton AC, Lindsey AW, Bernathy B, et al. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol.* 1957;189:609-15.
3. Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol.* 1954;179:261-7.
4. Solaro RJ. Mechanisms of the Frank-Starling law of the heart: the beat goes on. *Biophys J.* 2007;93:4095-6.
5. Fessler HE, Brower RG, Wise RA, et al. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis.* 1991;143:19-24.
6. Magder S. The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. *J Appl Physiol.* 2006;101:1523-5.
7. Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med.* 1998;26:1061-104.
8. Vincent JL, Rhodes A, Perel A, et al. Clinical review: Update on hemodynamic monitoring—a consensus of 16. *Crit Care.* 2011;15:229.

Section 2

Respiratory System

SECTION EDITOR: RAJESH CHAWLA

High Flow Oxygen Therapy: Current Status

Jose Chacko, Gagan Brar

INTRODUCTION

Supplemental oxygen is usually administered through nasal prongs or different types of masks. Although effective in correcting hypoxemia, these devices have considerable limitations. Inability to deliver sufficient flows in dyspneic patients is a major drawback. In respiratory failure, peak inspiratory flows may vary between 30–120 L/min;¹ however, the maximum flow achievable through conventional devices is 15 L/min, resulting in significant mismatch. This leads to a variable entrainment of atmospheric air and lack of control on the delivered fraction of inspired oxygen (FiO_2). Bubble humidifiers are commonly employed to humidify supplemental oxygen; however, the absolute humidity imparted by this technique is relatively poor.² Lack of adequate humidification of the inspired gas, delivered at less than optimal temperatures, leads to reduced water content of the mucus in the airways. This also reduces frequency of ciliary activity and slows down mucus clearance which may lead to inadequate clearing of secretions requiring increased physical effort to expel them.³ This is a significant problem in respiratory failure, often characterized by excessive secretions. Since the initial report by Dewan et al., there has been a growing interest in delivering adequately heated and humidified oxygen at high flows through nasal cannulae (HFNC).⁴ Currently there are several commercially available devices that deliver up to 60 L/min of fully conditioned gas at a fixed FiO_2 (Fig. 1). The system has a built-in, integrated flow generator and an air-oxygen blender that generates a preset FiO_2 . Humidification occurs through a heated passover humidifier. The heated and humidified mixture flows through a single limb corrugated tubing embedded with a heated wire that prevents loss of heat and condensation on its way to the patient end. The patient interface is a soft, wide bored nasal cannula that is capable of delivering a wide range of flows without gas jetting.

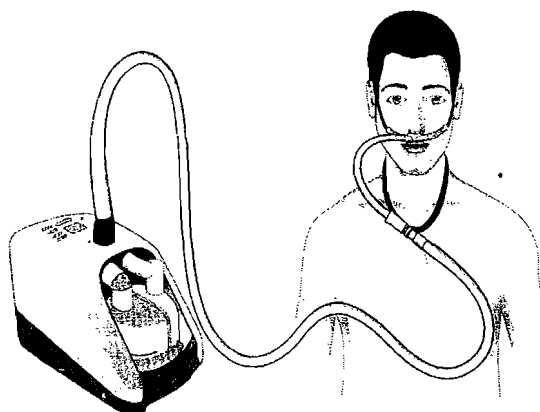


FIG. 1: The high flow nasal cannula device

SEARCH STRATEGY

For this systematic review, the authors searched PubMed using the key phrase “high flow nasal cannula”, setting a filter for “clinical trials”. The authors searched for additional articles on Embase, the Cochrane database of systematic reviews, and Google Scholar. Besides, reference lists of the retrieved articles and previous systematic reviews were searched manually.

MECHANISM

Constant Fraction of Inspired Oxygen

High flow nasal cannula delivers heated and humidified gas mixtures at flows up to 60 L/min, with FiO_2 ranging from 0.21 to nearly 1.0. At flow rates that match the peak inspiratory flow rate of patients in acute respiratory failure, there is minimal entrainment of atmospheric air, resulting in a constant, predictable FiO_2 .

Carbon Dioxide Washout

High gas flows lead to flush out of CO_2 from the nasopharynx, resulting in less rebreathing of dead space gas and better alveolar ventilation.⁵ Moreover, by reducing the partial pressure of carbon dioxide in the inspired gas, it raises the FiO_2 .⁶ Improved alveolar ventilation may result in better sense of comfort and lower respiratory rate.⁷

Expiratory Pressures

High flow nasal cannula results in generation of positive pressure in the airway in direct proportion to flow. With the mouth closed, end expiratory pressures of 7.4 cmH_2O at flows of 60 L/min have been demonstrated in human volunteers.⁸ In preoperative cardiac surgical patients, a mean end expiratory pressure of 2.7 cmH_2O was observed with the mouth closed at a flow of 35 L/min.⁹

Low level positive end expiratory pressure (PEEP) generated by HFNC may generate alveolar recruitment and increase the end expiratory lung volume; this may be more pronounced in obese subjects.¹⁰ In healthy adults, HFNC resulted in improved end expiratory lung volumes in both supine and prone positions, as reflected by change in end expiratory electrical impedance.¹⁰

Airway Resistance

The supraglottic airway includes a large distensible area in the nasopharynx that offers resistance to airflow.¹¹ Positive pressure during inspiration may splint the airways and thereby, reduce resistance to airflow. Besides, gas flows during inspiration that closely match peak inspiratory flow and may also contribute significantly to reduce inspiratory resistance. This might, in turn, help in decreasing the resistive work of breathing.¹²

Effects of Humidification

Warming and humidification of inspired gas require approximately 156 calories/min at a tidal volume of 500 mL and respiratory rate of 12/min. Delivery of preconditioned gas saves the energy expended in this manner and may significantly reduce the metabolic cost of breathing, and thereby, improve oxygenation.¹³ In addition, warming and humidification improve the subjective sense of comfort and reduces resistance to breathing. Humidification augments the aqueous content of the mucosal layer and consequently, improves ciliary activity and clearing of secretions.¹⁴

High Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure

Initial studies of HFNC in acute hypoxemic respiratory failure revealed favorable changes in physiological end

points such as oxygenation, respiratory rate, and degree of comfort.^{5,15} The first large randomized controlled trial (RCT) that addressed key clinical end points in acute hypoxic respiratory failure was the high flow oxygen therapy for resuscitation of acute lung injury (FLORALI) study.¹⁶ In a three-pronged trial, HFNC was compared with oxygen administration through a non-rebreather mask and noninvasive ventilation (NIV). There was no significant reduction in the need for endotracheal intubation and invasive ventilation with the use of HFNC. The intubation rate was lower than assumed for power calculation and hence a type II error may be a possibility. A post hoc analysis revealed a significantly lower rate of endotracheal intubation in a subgroup of patients with $\text{PaO}_2/\text{FiO}_2$ (P/F) ratios of less than 200. This raises the question whether more severely hypoxic patients might benefit with the use of HFNC; however, this hypothesis needs to be addressed in an adequately powered, controlled trial. 90-day mortality was lower in the HFNC group; however, this was a secondary end point, and hence, not powered to demonstrate a difference.

In an RCT of postoperative cardiothoracic and vascular surgical patients in acute hypoxemic respiratory failure, HFNC was compared with high flow oxygen through a face mask. Failure of therapy was defined as requirement for escalation of respiratory support within 24 hours of enrolment. Although HFNC resulted in fewer episodes of desaturation, there was no significant difference in the requirement for escalation to NIV between groups.¹⁷

High flow nasal cannula was used in patients with severe acute respiratory distress syndrome in a single-center observational study. Intubation rate was 40% in this study; a higher simplified acute physiology score II, occurrence of additional organ failure, lower P/F ratio and higher respiratory rate were significantly associated with an HFNC failure.¹⁸

Concerns have been raised if persisting too long with HFNC might lead to adverse clinical outcomes. In a propensity matched retrospective study, patients who required endotracheal intubation after failure of HFNC were analyzed. Earlier intubation, within 48 hours of HFNC use, was shown to be associated with significantly lower mortality compared to intubation after 48 hours.¹⁹

Post Extubation

Alveolar collapse and impaired gas exchange is a common feature after extubation of critically ill patients. Intuitively, HFNC with the ability to offer conditioned gases at a fixed, high FiO_2 might seem appealing in this situation. Earlier studies that primarily looked at physiological endpoints showed reductions in heart rate, respiratory rate, and dyspnea score,²⁰ but no difference in gas exchange.²¹ In an RCT of 105 patients with a P/F ratio of less than 300 just prior to extubation, HFNC was compared with ventimask for 48 hours after extubation.¹⁷ Discomfort related to the interface and dryness was significantly lower with fewer

episodes of desaturation in the HFNC group. Need for support with NIV and endotracheal intubation was significantly less with HFNC use. More robust evidence is needed before firm recommendations can be made for the use of HFNC in the post-extubation setting.

High Flow Nasal Cannula in Obese Patients

There is a sound physiological rationale behind the use of HFNC in obese subjects. High flows through nasal cannulae may provide splinting of easily collapsible upper airways in the obese; besides, the continuous positive airway pressure generated may recruit collapsed alveoli, thus increasing the functional residual capacity and the end expiratory lung volume. The end expiratory lung volume has been shown to increase in obese postoperative cardiac surgical patients with HFNC use. However, extubation to HFNC compared to standard oxygen therapy did not result in any improvement in lung collapse, oxygenation, respiratory rate or degree of dyspnea, as reported by patients.¹⁰ Further studies are required with the use of HFNC before any firm conclusion can be drawn in obese subjects.

Palliative Care

Noninvasive ventilation is commonly used in terminally ill patients to ease the subjective discomfort of dyspnea, where endotracheal intubation is considered inappropriate. However, this clearly impairs with communication and feeding. In a retrospective database analysis of 183 terminally ill cancer patients, HFNC resulted in improvement (41%) or continued stability (44%).²² Median time spent on HFNC was 3 days (range: 1–27). High flows through nasal cannulae was also employed in 50 patients with do-not-intubate and do-not-resuscitate orders.²³ The diagnosis included pulmonary fibrosis, pneumonia, chronic obstructive pulmonary disease (COPD), cancer, hematological malignancy, and congestive cardiac failure. Significant improvement in oxygen saturation and tachypnea was observed with 18% of patients progressing to NIV. Available evidence suggests that HFNC may be an appropriate therapy in terminally ill patients and has clear advantages over NIV in terms of retaining the ability to communicate and feeding.

Prior to Endotracheal Intubation

Significant hypoxia may ensue during attempts at intubation in critically ill patients.²⁴ Noninvasive ventilation may reduce the extent of desaturation and add to safety; however, interruption of mask application during intubation attempts may still lead to significant hypoxia. In a before-after study of over 800 patients, preoxygenation was compared between oxygen administration through a nonrebreather mask versus HFNC.²⁵ Median lowest saturation was significantly higher with HFNC (100 vs. 94%); patients who received

nonrebreather mask had significantly more episodes of hypoxia (14 vs. 2%). Besides, on multivariate analysis, the use of HFNC was an independent “protective factor” against the occurrence of severe hypoxemia. On the other hand, results of an RCT were contradictory.²⁶ Patients were randomized to receive “usual” preoxygenation, interrupted during laryngoscopy in the control arm, while uninterrupted HFNC at FiO₂ of 1.0 was administered in the intervention arm. There was no difference in the median lowest saturation, incidence of desaturation to <90%, 80%, or decrease by >3%. Duration of mechanical ventilation, ICU, and hospital stay were also similar between groups. Preoxygenation through bag and mask was compared with HFNC in another RCT. There was no difference in the primary outcome of lowest mean saturation between groups.²⁷ Clearly, no definite conclusions can be drawn regarding the efficacy of HFNC as a method of preoxygenation.

High Flow Nasal Cannula in Chronic Obstructive Airways Disease

High flow nasal cannula has several putative effects that may benefit patients with chronic obstructive airways disease. These include carbon dioxide washout from the nasopharyngeal dead space, modest levels of extrinsic PEEP, and improved mucous clearance resulting from optimal humidification. In a randomized crossover trial of 30 males with COPD on long-term oxygen therapy, oxygen at 2–4 L/min through a nasal cannula was compared with HFNC at a flow of 30 L/min.²⁸ In the HFNC-treated subjects, transcutaneous CO₂ levels were significantly lower; tidal volume was higher with a lower respiratory rate; besides, there was a significant increase in the end expiratory lung volumes. These physiological benefits in patients on long-term oxygen therapy suggest possibility of improved clinical outcomes and need further research, especially in acute exacerbations of COPD.

Bronchoscopy

Bronchoscopy in acutely ill patients is often associated with significant desaturation, especially if bronchoalveolar lavage is performed.²⁹ Noninvasive ventilation has been successfully employed to ameliorate the drop in oxygen saturation encountered during bronchoscopy.³⁰ In a three-pronged RCT, air entrainment mask at 40 L/min, HFNC at 40 L/min, and HFNC at 60 L/min were compared as methods of supplemental oxygen during bronchoscopy. The PaO₂ levels, P/F ratios and oxygen saturation were better in the HFNC 60 L/min group, compared to air entrainment mask or HFNC at 40 L/min. In another RCT, HFNC was compared to NIV in patients with acute hypoxemic respiratory failure undergoing flexible fiber optic bronchoscopy. Noninvasive application resulted in higher oxygen saturation before, during and after bronchoscopy. Available data do not support

the routine use of HFNC in critically ill patients requiring bronchoscopy.

META-ANALYSIS

The authors retrieved 43 articles in their initial PubMed search using the key phrase "high flow nasal cannula", with filter set for "clinical trials". Out of this, they identified eight RCTs.^{10,16,31-37} An additional RCT was identified through manual search of reference lists from previously retrieved articles.¹⁷ The authors performed a meta-analysis of these nine RCTs published till search date (Table 1). The outcomes of interest were: (i) the rate of escalation of respiratory support by intubation or reintubation (following initial extubation), or requirement for NIV support, as rescue therapy following initial use of HFNC and (ii) mortality at any reported time point. Studies were included if HFNC was compared with any form of conventional oxygen therapy device or NIV.

Nine articles provided data on intubation rates,^{16,17,31-37} and three on mortality.^{16,32,35} Eight studies compared HFNC to standard oxygen therapy;^{10,16,17,31,32,35,36} one of these compared HFNC with standard oxygen therapy and NIV in a three-armed trial.¹⁶ In another study, HFNC was compared to NIV in patients who failed a spontaneous breathing trial

or failed extubation after cardiothoracic surgery.³³ Pooled analysis revealed a significantly lower rate of escalation of respiratory support with the use of HFNC [odds ratio (OR) = 0.52; confidence interval (CI) 0.32–0.84; $p = 0.008$; p for heterogeneity = 0.005, $I^2 = 64\%$] (Fig. 2).

Three studies reported mortality rates^{16,32,35} and two reported hospital mortality.^{32,35} One study reported 90-day mortality.¹⁶ On pooled analysis, there was no significant difference in mortality between HFNC and standard oxygen therapy (OR = 0.72; CI 0.42–1.24; $p = 0.24$; p for heterogeneity = 0.26, $I^2 = 26\%$) (Fig. 3).

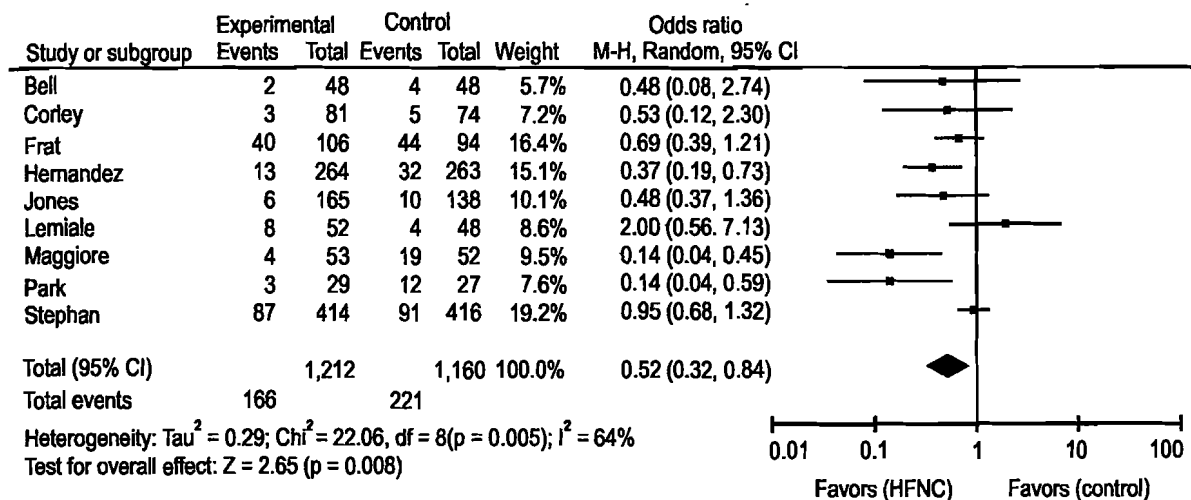
CONCLUSION

Fully humidified, warmed gas at a fixed FiO_2 can be delivered through HFNC. Apart from its putative beneficial physiological effects, it may also lead to improved clinical outcomes. Evidence suggests that it may help to reduce the rate of escalation of respiratory support in acute hypoxemic respiratory failure, especially in patients with low P/F ratios. As with NIV, persistence for too long may lead to delay in intubation and adverse clinical outcomes. High flows through nasal cannulae may have a role in patients at risk of reintubation and in those with a failed spontaneous

TABLE 1 Summary of studies included in the meta-analysis

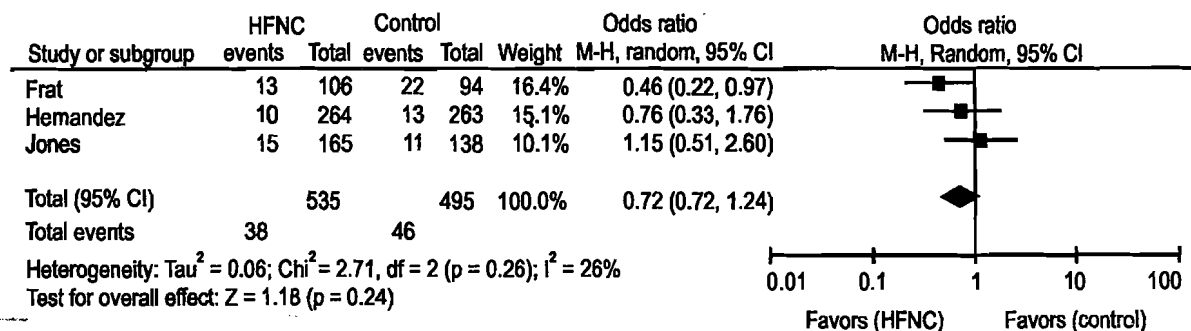
Author, year	Setting	Comparator	Main results
Bell, 2015	Breathless patients with respiratory rate >25/min, and $SpO_2 < 93\%$, in the emergency department	Standard oxygen therapy	Less patients required escalation of respiratory support with HFNC
Corley, 2015	BMI >30 kg/m ² , post extubation after cardiac surgery under cardiopulmonary bypass	Standard oxygen therapy	No difference in requirement for escalation of respiratory support
Frat, 2015	Acute hypoxemic respiratory failure, three-armed study	Noninvasive ventilation or oxygen through a non-rebreather mask	No difference in intubation rates between groups. On post hoc analysis, reduced intubation rate with HFNC in patients with P/F ratio <200. Less 90 day mortality with HFNC. More ventilator free days with HFNC.
Hernández, 2016	Post extubation in patients at low risk for reintubation	Standard oxygen therapy	Lower reintubation rates with HFNC at 72 h. Respiratory failure less common with HFNC.
Jones, 2016	Acute hypoxemic respiratory failure in the emergency department	Standard oxygen therapy	No difference in the requirement for invasive ventilation or NIV.
Lemiale, 2015	Immunosuppressed patients with hypoxemic respiratory failure	Standard oxygen therapy	No difference in the requirement for invasive ventilation or NIV.
Maggiore, 2014	Post extubation	Standard oxygen therapy	Lower reintubation and NIV rates with HFNC.
Parke, 2008	Mild to moderate hypoxemic respiratory failure	Standard oxygen therapy	More patients on HFNC succeeded with allocated treatment.
Stephan, 2015	Postoperative cardiothoracic surgical patients. Acute respiratory failure or deemed at risk of acute respiratory failure after extubation	NIV (BIPAP)	No difference in the failure of allocated treatment. No difference in ICU mortality.

HFNC, high flow nasal cannula; BMI, body mass index; ICU, intensive care unit; SpO_2 , arterial oxygen saturation, P/F ratio, partial pressure arterial oxygen and fraction of inspired oxygen ratio; NIV, noninvasive ventilation; BIPAP, bilevel positive airway pressure.



HFNC, high flow nasal cannula; CI, confidence interval; M-H, Mantel-Haenszel.

FIG. 2: Requirement for escalation of respiratory support: high flow nasal cannula versus standard oxygen therapy



HFNC, high flow nasal cannula; CI, confidence interval; M-H, Mantel-Haenszel.

FIG. 3: Mortality at any reported time point: high flow nasal cannula versus standard oxygen therapy

breathing trial prior to extubation. It may be a valuable adjunct in terminally ill patients as part of palliative care—with the obvious advantages of better comfort and ability to communicate compared to NIV. HFNC may also reduce the incidence desaturation during bronchoscopy in critically ill patients. The use of HFNC cannula may maintain oxygen saturation and protect against hypoxic episodes better compared to conventional methods of preoxygenation prior to intubation. Efficacy in morbidly obese patients needs further evaluation. Although intuitively beneficial in acute exacerbations of COPD, controlled studies are required to substantiate this.

REFERENCES

1. L'Her E, Deye N, Lellouche F, et al. Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med*. 2005;172(9):1112-8.
2. Chanques G, Constantin JM, Sauter M, et al. Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. *Intensive Care Med*. 2009;35(6):996-1003.
3. Kilgour E, Rankin N, Ryan S, et al. Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. *Intensive Care Med*. 2004;30(7):1491-4.
4. Dewan NA, Bell CW. Effect of low flow and high flow oxygen delivery on exercise tolerance and sensation of dyspnea. A study comparing the transtracheal catheter and nasal prongs. *Chest*. 1994;105(4):1061-5.
5. Sztymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med*. 2011;37(11):1780-6.
6. Spence CJ, Buchmann NA, Jermy MC. Unsteady flow in the nasal cavity with high flow therapy measured by stereoscopic PIV. *Exp Fluids*. 2012;52(3):569-79.
7. Schmidt M, Banzett RB, Raux M, et al. Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients. *Intensive Care Med*. 2014;40(1):1-10.
8. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care*. 2007;20(4):126-31.
9. Riera J, Pérez P, Cortés J, et al. Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. *Respir Care*. 2013;58(4):589-96.
10. Corley A, Bull T, Spooner AJ, et al. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥ 30 : a randomised controlled trial. *Intensive Care Med*. 2015;41(5):887-94.
11. Shepard JW, Burger CD. Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1990;142(6 Pt 1):1288-93.
12. Ricard JD. High flow nasal oxygen in acute respiratory failure. *Minerva Anesthesiol*. 2012;78(7):836-41.
13. Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: mechanisms of action. *Respir Med*. 2009;103(10):1400-5.

14. Sim MA, Dean P, Kinsella J, et al. Performance of oxygen delivery devices when the breathing pattern of respiratory failure is simulated. *Anaesthesia*. 2008;63(9):938-40.
15. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55(4):408-13.
16. Frat JP, Thille AW, Mercat A, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. *N Engl J Med*. 2015;372(23):2185-96.
17. Maggiore SM, Idrone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282-8.
18. Messika J, Ben Ahmed K, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: A 1-year observational study. *Respir Care*. 2015;60(2):162-9.
19. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med*. 2015;41(4):623-32.
20. Rittayamai N, Tscheikuna J, Rujiwit P. High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study. *Respir Care*. 2014;59(4):485-90.
21. Tiruvoipati R, Lewis Det, Haji K, et al. High-flow nasal oxygen vs high-flow face mask: a randomized crossover trial in extubated patients. *J Crit Care*. 2010;25(3):463-8.
22. Epstein AS, Hartridge-Lambert SK, Ramaker JS, et al. Humidified high-flow nasal oxygen utilization in patients with cancer at Memorial Sloan-Kettering Cancer Center. *J Palliat Med*. 2011;14(7):835-9.
23. Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. *Respir Care*. 2013;58(4):597-600.
24. Jaber S, Amraoui J, Lefrant JY, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med*. 2006;34(9):2355-61.
25. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med*. 2015;43(3):574-83.
26. Semler MW, Janz DR, Lentz RJ, et al. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med*. 2016;193(3):273-80.
27. Simon M, Wachs C, Braune S, et al. High-Flow Nasal Cannula Oxygen Versus Bag-Valve-Mask for Preoxygenation Before Intubation in Subjects With Hypoxemic Respiratory Failure. *Respir Care*. 2016;61(9):1160-7.
28. Fraser JF, Spooner AJ, Dunster KR, et al. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax*. 2016;71(8):759-61.
29. Papazian L, Colt HG, Scemama F, et al. Effects of consecutive protected specimen brushing and bronchoalveolar lavage on gas exchange and hemodynamics in ventilated patients. *Chest*. 1993;104(5):1548-52.
30. Antonelli M, Pennisi MA, Conti G, Bello G, Maggiore SM, Michetti V, et al. Fiberoptic bronchoscopy during noninvasive positive pressure ventilation delivered by helmet. *Intensive Care Med*. 2003;29(1):126-9.
31. Parke RL, McGuinness SP, Eccleston ML. A Preliminary Randomized Controlled Trial to Assess Effectiveness of Nasal High-Flow Oxygen in Intensive Care Patients. *Respir Care*. 2011;56(3):265-70.
32. Hernández G, Vaquero C, González P, et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. *JAMA*. 2016;315(13):1354-61.
33. Stéphan F, Barrucand B, Petit P, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. *JAMA*. 2015;313(23):2331-9.
34. Bell N, Hutchinson CL, Green TC, et al. Randomised control trial of humidified high flow nasal cannulae versus standard oxygen in the emergency department. *Emerg Med Australas*. 2015. doi: 10.1111/1742-6723.12490.
35. Jones PG, Kamona S, Doran O, et al. Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study. *Respir Care*. 2016;61(3):291-9.
36. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care*. 2015;19:380.
37. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth*. 2011;107(6):998-1004.

Oxygen Reserve Index

Subhash Todi

INTRODUCTION

In spite of universal availability, miniaturization, and use of pulse oximetry in all healthcare delivery situations, unanticipated hypoxemia is not very infrequent even in patients on supplemental oxygen. These situations are common, especially in postoperative recovery room, certain surgeries like bariatric surgery, transporting critically ill patient, and in intensive care unit. Patients in extremes of age, compromised lung function, and multiple comorbidities are also prone to these complications. The response to this unanticipated hypoxia is to increase the inspired oxygen concentration, but single or repeated episodes of unanticipated hypoxia even for a brief duration may be detrimental to patients with compromised organ function and may have short- or long-term consequences. A technology which will alert physicians of impending hypoxia, especially who are on supplemental oxygen, will be immensely helpful in these clinical situations.

The pulse oximeter as is currently used in clinical practice has revolutionized the practice of clinical medicine and is regarded as the fifth vital sign. There are certain inherent limitations of the current technology of pulse oximetry. Firstly, it is inaccurate at the lower end of oxygen saturation, below 80% arterial oxygenation (PaO_2) cannot be reliably predicted at this range. On the other hand, due to the sigmoid shape of oxygen dissociation curve, the arterial oxygen saturation measured by pulse oximetry (SpO_2) reads 100% at a PaO_2 of 100 mmHg and cannot reflect oxygenation status beyond this point as the dissociation curve flattens out. Any further increase in PaO_2 cannot be monitored by the present generation of oximeters.

There is a clinical need in some circumstances (Box 1) for monitoring PaO_2 between 100 and 200 mmHg where the current pulse oximetry is not useful as it will show a saturation of 99–100% whether PaO_2 is 100 or 200 mmHg. A fall of PaO_2 from 200 to 100 mmHg will not be reflected by the current pulse oximeters. Oxygen reserve index (ORI) is

Box 1: Clinical situations where oxygen reserve index assessment will be helpful

- Preoxygenation
 - During rapid sequence intubation
 - In critically ill patients with compromised lung function
 - Prior to intubation in patients on noninvasive ventilation
 - Patients at risk for prolonged intubation time due to difficult airway
- Early warning of hypoxemia
 - In patients on supplemental oxygenation
 - Intraoperatively in bariatric, orthopedic (during cementing), or back surgery
 - During recruitment maneuvers
 - During endotracheal suctioning
- Hypoxemia due to carbon dioxide retention
 - In patients on supplemental oxygen with obstructive airway disease
- Avoid hyperoxemia
 - Post cardiac arrest
 - Acute respiratory distress syndrome
- Permissive hyperoxemia
 - In severe anemia
 - Septic shock

a novel concept that will warn the physician of impending hypoxemia or a hyperoxic state.

CLINICAL SITUATIONS WHERE OXYGEN RESERVE INDEX MAY BE HELPFUL

Preoxygenation

Intubation is usually a lengthy procedure in intensive care unit (ICU) with a potential risk of desaturation during the procedure. Even a brief period of desaturation may be detrimental in critically ill patient with compromised cardiorespiratory status. In these patients who are usually

hypoxemic to begin with, oxygen reserves are not sufficient to cover the lengthy duration of intubation. Preoxygenation has become routine as an intubation protocol in ICU.¹ This can be achieved by administering near 100% oxygen from a nonrebreathing face mask and spontaneous breathing, manual bag mask ventilation by 100% oxygen or noninvasive ventilation. The aim is to create an oxygen buffer zone and to keep arterial PaO_2 above 150 mmHg to prevent unanticipated hypoxia. Duration of apnea without desaturation is more common in obese, pregnant, and patients with increased metabolism. Time of drop of SpO_2 below 90% (tolerable apnea time) can be extended up to almost 10 minutes after 3 minutes of classic preoxygenation by attaining a supranormal arterial oxygenation during preoxygenation procedure. This provides valuable additional time to secure the airway and make the intubation procedure safer.²

Inadequate preoxygenation, defined as expired oxygen fraction (FeO_2) above 90% is disappointingly common in clinical practice. In a prospective study of 1,050 consecutive preoperative patients in whom preoxygenation was performed for 3 minutes with a facial mask, inadequate preoxygenation was observed in 56% of patients. The independent risk factors for inadequate preoxygenation were similar to those previously identified for difficult face mask ventilation.³

In clinical practice, it is difficult to measure FeO_2 to ascertain adequacy of preoxygenation and one has to rely on a conventional pulse oximetry reading of 100% saturation as a surrogate. This strategy might miss those patients who are in the range of 100–150 mmHg of arterial PaO_2 showing 100% SpO_2 on the conventional pulse oximetry and are still at risk for hypoxemia during prolonged intubation process due to lack of oxygen buffer. A noninvasive technology, like ORI, to ascertain PaO_2 in the range of 150–250 mmHg to ensure adequate oxygen buffer prior to intubation especially in at risk patient population, will be immensely helpful to practitioners.

Other clinical situations where measuring ORI will be helpful as a marker of adequate preoxygenation will be emergency rapid sequence intubation and prior to endotracheal suctioning in mechanically ventilated patient.⁴

Early Warning of Impending Hypoxemia

In acutely ill patient with compromised lung function, it is advisable to keep SpO_2 around 95% reflecting a PaO_2 of 60 mmHg, so that any further deterioration in oxygenation may be detected rapidly by a fall of SpO_2 as this value of PaO_2 is at the “desaturation cliff” of oxyhemoglobin dissociation curve. This strategy have a downside as there is no oxygen buffer and any further deterioration of lung function will expose the patient to hypoxia before correctable measures are taken. On the other hand, keeping a SpO_2 of 98% and above may not reflect deteriorating oxygenation status, though still

in the normal range as example from 200 to 100 mmHg, as conventional pulse oximeter will continue to show adequate saturation above 98% during this time. A noninvasive technology that could give an indication of the fall of PaO_2 while still in the normal range would be useful in clinical practice.

Another clinical situation where early warning of impending hypoxemia may be helpful is in intraoperative settings where certain maneuvers, like cementing during orthopedic procedures, body positioning for back surgery, etc., may be associated with sudden ventilation perfusion mismatch and hypoxia. A priori knowledge of oxygen buffer in these situations and adequate preoxygenation may avoid these inadvertent hypoxemic episodes.

Oxygen reserve index may also help during recruitment maneuver or positive end-expiratory pressure titration, where once oxygen saturation has reached the upper limit, further improvement in the oxygenation can only be noted by repeated arterial blood gas analysis. Similarly, improving respiratory status in acute respiratory distress syndrome (ARDS) can also be identified early with this technique once the oxygen saturation reaches high normal values, allowing early downward titration of FiO_2 .

Hypoventilation on Supplemental Oxygen

Another potential limitation of conventional pulse oximetry in patients on supplemental oxygenation is detecting hypoventilation with carbon dioxide (CO_2) retention which can occur during recovery from anesthesia, procedural sedation, opioid analgesic use, etc. In these circumstances of hypercapnic respiratory compromise, the SpO_2 will continue to show above 98% as the patient is on supplemental oxygen though arterial PaO_2 will decline from 200 mmHg downwards due to alveolar CO_2 accumulation at the cost of decreasing alveolar oxygen content.⁵ A technology which can preempt falling arterial oxygen in these clinical situations may prompt an arterial blood gas analysis to rule out hypercapnia as a primary cause of hypoxemia, and not supplemental oxygen but proper ventilation as the adequate remedy may be instituted.

Hyperoxemia Detection

Traditionally, hypoxia has been the main target of oxygen resuscitation and application of supplemental oxygen is ubiquitous in hospitalized patients even if they are normoxic. Excess of oxygen may have deleterious effect through the formation of reactive oxygen species and oxygen free radicals within mitochondria which are cytotoxic. In a multicenter cohort study of 6,326 nontraumatic cardiac arrest patients, hyperoxia ($\text{PaO}_2 > 300$ mmHg) on arrival to ICU had a significantly higher inhospital mortality of 63%, compared with the hypoxia group ($\text{PaO}_2 < 60$ mmHg or $\text{PaO}_2/\text{FiO}_2$ ratio

of <300 mmHg) of 57% and normoxia group of 45%.⁶ The hypothesis being that ischemia reperfusion injury promotes formation of reactive oxygen species in presence of hypoxia which is injurious to tissues. In experimental models of the ARDS, susceptibility to oxygen toxicity is increased due to coexisting lung inflammation. In these situations, aiming for normoxia may lead to inadvertent high oxygen exposure to the lung with consequent deleterious effects.⁷ Critical care and anesthesia literature have also recently highlighted these deleterious effects of hyperoxia.⁸ Due to these observations, current guidelines recommend to keep SpO₂ around 92% using the lowest FiO₂ possible.⁹

Contrary to the above recommendations, there are also observations that target oxygen should be in the higher range as a strategy to improve long-term neurocognitive and physical deconditioning outcome of ARDS survivors.¹⁰ Hyperoxia has also been described to be beneficial in patients with severe anemia and in septic shock to improve the oxygen delivery for better tissue oxygenation.^{11,12}

Thus, there are conflicting results in the literature regarding the right level of desired arterial oxygen level.^{13,14} In clinical practice, clinicians tend to err on the side of safety and provide more oxygen than necessary. In a retrospective database analysis of 1,26,778 arterial blood gas tests from 5,498 mechanically ventilated patients, PaO₂ was above 120 mmHg in 22% of observations while FiO₂ was decreased in only 25% of these patients. Moreover, hyperoxia was accepted without adjustment in ventilator settings if FiO₂ was 0.4 or lower.¹⁵

In the above circumstances, having a continuous noninvasive measurement of oxygenation in the hypoxic, normoxic, and hyperoxic range is highly desirable to fine tune the delivered oxygen level and individualize patient management. In clinical situations where inadvertent hypoxemia needs to be avoided, keeping an ORI of 1 will be helpful. On the other hand, where hyperoxemia needs to be avoided, ORI should be kept below 0.5. This tool is likely to become a useful adjunct to pulse oximetry which can be utilized in various clinical scenarios as mentioned above.

TECHNOLOGY

Using seven infrared wavelengths of light and calculating differential absorption and optically detecting changes in mixed venous oxygen saturation (SvO₂) after arterial oxygen saturation (SaO₂) has saturated to the maximum is a novel pulse oximeter-based nondimensional index that ranges from 1 to 0 as PaO₂ decreases from about 200 to 80 mmHg. A value of ORI of 0.3 has a sensitivity of 80% and specificity of 85% to detect PaO₂ of 150 mmHg. Decreases in ORI to near 0.24 may provide advance indication of falling PaO₂ approaching 100 mmHg when SpO₂ is above 98%. A good oxygen reserve is indicated by an ORI 0.8 or above reflecting a PaO₂ of 200 mmHg¹⁶ (Table 1).

TABLE 1 Relationship of oxygen reserve index and arterial partial pressure of oxygen

ORI	PaO ₂ (mmHg)	SpO ₂ (%)
>0.24	>100	>98
>0.55	>150	100

ORI, oxygen reserve index; PaO₂, arterial partial pressure of oxygen; SpO₂, arterial oxygen saturation measured by pulse oximetry

CLINICAL STUDIES

In a study conducted in 25 pediatric elective surgical patients during induction of anesthesia after preoxygenation, induction of anesthesia, and endotracheal intubation, the anesthesia circuit was disconnected and oxygen saturation was allowed to decrease to 90% before recommencing ventilation. The ORI and SpO₂ values were recorded at the beginning of apnea, beginning and end of endotracheal intubation, beginning and end of the ORI alarm, and 2 minutes after reoxygenation. During apnea, the ORI progressively decreased over a mean of 5.9 ± 3.1 minutes from 0.73 ± 0.16 at the beginning of apnea to 0.37 ± 0.11 . The SpO₂ remained 100% throughout this initial period. The ORI alarm activation was associated with oxygen saturation decrease to 98% in median of 31.5 seconds (interquartile range, 19–34.3 s). The conclusion from this pilot study was that ORI detected impending desaturation in median of 31.5 seconds (interquartile range, 19–34.3 s) before noticeable changes in SpO₂ occurred. This might represent a clinically important warning time, which will give clinicians time for corrective actions.¹⁷

In another study of 106 adult patients undergoing elective surgery, ORI with PaO₂ were measured serially and regression analysis was performed for ORI values corresponding to PaO₂ of 100 and 150 mmHg. Regression analysis showed that the ORI to PaO₂ relationship was more stronger for PaO₂ till 240 mmHg ($r = 0.536$) than for PaO₂ over 240 mmHg ($r = 0.0016$). Measured PaO₂ was ≥ 100 mmHg for all ORI over 0.24. Measured PaO₂ was ≥ 150 mmHg in 96.6% of samples when ORI was over 0.55. These findings suggest that ORI above 0.24 can distinguish PaO₂ ≥ 100 mmHg when SpO₂ is over 98% and ORI above 0.55 appears to be a threshold to distinguish PaO₂ ≥ 150 mmHg. The other way of looking at this data is decreases in ORI to near 0.24 may provide advance indication of falling PaO₂ approaching 100 mmHg when SpO₂ is above 98%. A prospective study was proposed to observe the clinical utility of interventions based on continuous ORI monitoring.¹⁸

CONCLUSION

Oxygen reserve index is a reliable indicator for assessing PaO₂ in the range of 100–200 mmHg. This assessment is

useful to avoid inadvertent hypoxemia (>200 mmHg) and also serve as an early warning of impending hypoxemia (<100 mmHg) where the conventional pulse oximetry is not useful. Judicious use of ORI in patients on supplemental oxygen will be an useful adjunct to conventional pulse oximetry for noninvasive continuous monitoring of oxygen status. It will also avoid the need for repeated arterial blood gas analysis in situations where arterial oxygen status above 100 mmHg needs to be ascertained.

REFERENCES

1. Bourroche G, Bourgain JL. Preoxygenation and general anesthesia: a review. *Minerva Anesthesiol.* 2015;81(8):910-20.
2. Tanoubi I, Drolet P, Donati F. Optimizing preoxygenation in adults. *Can J Anaesth.* 2009;56(6):449-66.
3. Baillard C, Depret F, Levy V, et al. Incidence and prediction of inadequate preoxygenation before induction of anaesthesia. *Ann Fr Anesth Reanim.* 2014;33(4):e55-8.
4. Gebremedhn EG, Mesele D, Aemero D, et al. The incidence of oxygen desaturation during rapid sequence induction and intubation. *World J Emerg Med.* 2014;5(4):279-85.
5. Fu ES, Downs JB, Schweiger JW, et al. Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. *Chest.* 2004;126(5):1552-8.
6. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA.* 2010;303(21):2165-71.
7. Aggarwal NR, Brower RG. Targeting normoxemia in acute respiratory distress syndrome may cause worse short-term outcomes because of oxygen toxicity. *Ann Am Thorac Soc.* 2014;11(9):1449-53.
8. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Bench-to-bedside review: the effects of hyperoxia during critical illness. *Crit Care.* 2015;19:284.
9. Jubran A. Pulse oximetry. *Crit Care.* 2015;19:272.
10. Mikkelsen ME, Anderson B, Christie JD, et al. Can we optimize long-term outcomes in acute respiratory distress syndrome by targeting normoxemia? *Ann Am Thorac Soc.* 2014;11(4):613-8.
11. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. *Intensive Care Med.* 2015;41(6):1118-21.
12. Lauscher P, Mirakaj V, Koenig K, et al. Why hyperoxia matters during acute anemia. *Minerva Anesthesiol.* 2013;79(6):643-51.
13. Hafner S, Beloncle F, Koch A, et al. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care.* 2015;5(1):42.
14. Martin DS, Grocott MP. Oxygen therapy in anaesthesia: the yin and yang of O₂. *Br J Anaesth.* 2013;111(6):867.
15. de Graaff AE, Dongelmans DA, Binnekade JM, et al. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO₂. *Intensive Care Med.* 2011;37(1):46-51.
16. Applegate R, Dorotta I, Applegate P. Relationship between oxygen reserve index and arterial partial pressure of oxygen during surgery. *Anesth Analg.* 2015;120 (Suppl 1):S-377.
17. Szmuk P, Steiner JW, Olomu PN, et al. Oxygen reserve index: A novel noninvasive measure of oxygen reserve—A pilot study. *Anesthesiology.* 2016;124(4):779-84.
18. Applegate RL 2nd, Dorotta IL, Wells B, et al. The relationship between oxygen reserve index and arterial partial pressure of oxygen during surgery. *Anesth Analg.* 2016.

End-tidal Carbon Dioxide: What's New?

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INTRODUCTION

Capnography refers to the measurement and display of carbon dioxide (CO_2) concentrations in respiratory gases. From 1990 onwards, there is a broad appreciation of its value in ensuring proper endotracheal tube (ETT) placement; it is also used to guide tidal volume and rate settings during mechanical ventilation. However, capnogram gives more information than is generally appreciated. A full appreciation of capnography is based on the physiology of CO_2 exchange in the lung.¹

CAPNOMETRY: CURRENT TECHNOLOGIES

Measurement of fraction of end-tidal CO_2 in the expired air at the airway opening is referred to as capnometry. The graphic representation and display of this measurement over time is referred to as capnography. Infrared light absorption or mass spectrometry technology both of which is reliable and relatively accurate is utilized for these measurements. Sampling techniques of expired air which are used for these measurements are either mainstream or sidestream sampling. An airway adaptor cuvette that incorporates an infrared light source and CO_2 sensor is attached in-line and close to the ETT in the mainstream sampling. A T-piece adapter is placed at the airway opening, through which expired air is continually aspirated for analysis in sidestream sampling.²

CURRENT CLINICAL APPLICATIONS

Capnography and Cardiac Output

It has been shown that end-tidal carbon dioxide (EtCO_2) values change with return of spontaneous circulation (ROSC) postcardiac arrest, during passive leg raising (PLR) and in many shock states. Short-term studies have

shown a direct relationship between cardiac output and time capnography. These changes may not be always consistent, because in steady state, the volume of CO_2 exhaled through the lungs must equal that produced in the tissues metabolically, regardless of cardiac output. Cardiac output largely affects EtCO_2 only in dynamic situations, not when the circulation is stable.² The appearance of a direct relationship between cardiac output and EtCO_2 relates to nonsteady-state conditions combined with the fact that the body can store large amounts of CO_2 . For example, if cardiac output is reduced through hemorrhagic shock, EtCO_2 falls transiently as less CO_2 returns to the lungs.

As the cardiac output falls, tissue and venous partial pressure of CO_2 (PCO_2) rise, ultimately, restoring the total volume of CO_2 reaching the lungs and balancing metabolic production with excretion. Because a large amount of CO_2 can be stored in the body as tissue CO_2 rises, equilibrium will not be reached quickly. In addition, many interventions to change cardiac output also change dead space (for example, by raising or lowering left atrial pressure). Although EtCO_2 does not reflect cardiac output directly, by signaling changes, it has great value during resuscitation and when judging fluid responsiveness.

Adjusting Ventilatory Settings

Time capnography offers an attractive alternative to arterial blood gas analysis because it is continuous and noninvasive in adjusting ventilator settings. End-tidal CO_2 values may exceed partial arterial pressure of CO_2 (PaCO_2) or be much lower.³ When ventilator settings are adjusted, the changes in EtCO_2 and PaCO_2 are poorly related, even moving in opposite directions.

This is not surprising when all of the determinants of EtCO_2 are considered. For example, augmenting the ventilator rate or tidal volume should lower both EtCO_2 (because it tends to raise the ratio of alveolar ventilation to

CO_2 production) and PaCO_2 , but if the dead space fraction rises, EtCO_2 may fall while PaCO_2 rises. As positive end-expiratory pressure affects alveolar dead space, its value affects the capnogram; moreover, these effects have been used to guide positive end-expiratory pressure levels in acute respiratory distress syndrome. These data show that relying on EtCO_2 as a surrogate for PaCO_2 may lead to serious error.

Nevertheless, whereas ventilator waveforms offer similar monitoring, capnography remains important during mechanical ventilation to ensure airway patency and detect dislodgment or disconnection of the ETT.⁴ It probably has a more important role during patient transport when the risk of ETT migration is even higher.

Detecting Pulmonary Embolus

Pulmonary embolism (PE) remains a diagnostic challenge in the intensive care unit (ICU). Risks involved in transport and risk of acute kidney injury make computed tomography (CT) angiography a cumbersome screening test in critically ill patients. Pulmonary embolism compromises perfusion of the affected alveoli with much less impact on ventilation, which suggests that capnography could be diagnostically useful.

Based on the physiological changes, one would expect PE to: (i) raise the alveolar dead space (and thus, the physiologic and alveolar dead space fractions), (ii) lower the expired CO_2 value throughout phase III and widen any gradient between PaCO_2 and EtCO_2 (since gas expired from high-V/Q alveoli has little CO_2), and (iii) not raise the phase III slope [perhaps allowing distinction from chronic obstructive pulmonary disease (COPD) and other airway diseases with marked V/Q heterogeneity].

The diagnostic use of capnography for suspected PE has several limitations. First, most clinical data pertain to volume capnography; time capnography does not give idea about dead space. Secondly, PE may perturb the circulation, causing changes in CO_2 delivery to the lung that invalidate the assumption of steady state. Thirdly, most studies have been conducted on stable patients in the emergency department (ED) rather than those who were mechanically ventilated in an ICU.

Finally, since changes in ventilator settings or patient ventilator interaction can change the capnographic waveform, artifacts of care must not be confused with signals of pathology. Nevertheless, capnogram may provide supportive clues to potentiate the suspicion of PE, especially when clubbed with D-dimer value.⁵

Indicator of Thrombolysis in Massive Embolism

During thrombolysis, increase in pulmonary perfusion causes the decrease in the P(a-Et)CO_2 and there will be recovery of right ventricular function. These results were interpreted as a successful thrombolysis.⁶

Obstructive Lung Diseases

Obstructive lung diseases are characterized by widely varying V/Q ratios, producing typical capnographic signatures. The phase II transition from anatomic dead space to alveolar gas is blurred by the early contribution from high V/Q units (with low PaCO_2), which tends to reduce the steepness of its rise.

During phase III, units with varying V/Q ratios continue to empty in desynchronized fashion (higher V/Q regions that have lower PaCO_2 contribute more earlier, whereas lower V/Q regions with higher PaCO_2 dominate later), amplifying the rise of the plateau phase. This combination causes the alpha angle between phases II and III to increase.⁷ In severely obstructive diseases, the capnogram assumes a shark-fin appearance. The steeper phase III also causes the end-tidal value to depend more strongly on expiratory time. Combined with the anatomic dead space inherent in emphysema, this feature causes marked discrepancies between end-tidal and arterial PCO_2 values.

These qualitative features of obstructive diseases on time capnography correspond to quantitative aspects on volume capnography. An increased phase III slope has been demonstrated in most diseases with airflow obstruction (COPD, asthma, and bronchiectasis). The degree of slope correlates with the severity of airflow obstruction measured by spirometry and the degree of emphysema seen on chest CT images.⁸

Automated analysis of multiple capnographic indices may increase the sensitivity and specificity for diagnosing obstructive lung disease. A combination of exhalation duration, EtCO_2 , end-exhalation slope, and time spent at EtCO_2 succeeds in distinguishing patients with COPD from those with congestive heart failure. End tidal CO_2 may differ markedly from the simultaneous PaCO_2 , especially in patients who have obstructive disease and this is true when patients are stable or are experiencing an exacerbation.

Slow, forced maximal expiration can produce a much better correlation between EtCO_2 and PaCO_2 , but this procedure is not practical in critically ill patients.⁹ In some patients with COPD who receive mechanical ventilation, the difference between EtCO_2 and PaCO_2 can exceed 40 mmHg, which emphasizes the serious errors that can be made in drawing inferences about the adequacy of ventilation based on EtCO_2 values.

Capnography during Nonsteady-state Conditions-Cardiopulmonary Resuscitation

During cardiac arrest, capnography signifies increasing pulmonary blood flow and thus the adequacy of chest compressions. An EtCO_2 value of <10 mmHg after 20 minutes of cardiopulmonary resuscitation (CPR) is associated with very high mortality. Similarly, if EtCO_2 is persistently low, the patient is unlikely to have ROSC.⁹

A drop in EtCO_2 can indicate rescuer fatigue or an inappropriate chest compression rate or depth. Cardio-pulmonary resuscitation is frequently interrupted to examine the patient for a return of pulse and to analyze the rhythm. Such interruptions are known to be detrimental, as they dissipate the coronary perfusion pressure that is critical to successful resuscitation. With capnography, interruptions can be eliminated because ROSC and a rise in cardiac output will be signaled by a sharp rise in EtCO_2 . Since time capnography is currently available on most defibrillators and in the ICU, it is time to integrate our understanding of capnographic physiology into the realm of resuscitation.¹⁰

Predicting Fluid Responsiveness

There is increasing recognition that many patients in shock fail to respond to a fluid bolus. Since empirical fluid administration may be harmful, current practice emphasizes prediction of fluid responsiveness to guide therapy. Passive leg raising is a highly sensitive and specific indicator of subsequent fluid response, but it depends on some measure of effect, typically real-time echocardiography. End tidal CO_2 has been shown to provide a technically simpler alternative in patients who are mechanically ventilated without respiratory effort. In patients who are responsive to fluids, EtCO_2 rises by at least 5% with PLR, outperforming changes in arterial pulse pressure as a clinically useful predictor.¹¹

Procedural Sedation

Sedation and analgesia are increasingly administered by nonanesthesiologists for endoscopy, bronchoscopy, and other procedures. Moderate sedation frequently progresses inadvertently to deeper sedation and can lead to hypoventilation or apnea, airway obstruction or laryngospasm, and hypoxemia, especially in obese people or in patients with sleep apnea. Sedatives and analgesics can precipitate these complications, all of which have distinct capnographic findings. Several studies show that capnography is more sensitive than clinical monitoring, oximetry, or visual assessment in detecting respiratory depression in patients receiving moderate procedural sedation.¹²

Use of Capnometry to Verify Feeding Tube Placement

A study was conducted on 53 mechanically ventilated patient on enteral feed to validate the use of capnometry to confirm appropriate tube placement. The feeding tube was initially inserted to 30 cm length and the EtCO_2 detector was attached to the proximal end of the feeding tube. After a minute, any change in color was observed. If the placement

was appropriate, the color remained purple but changed to tan or yellow if CO_2 was detected, interpreted as airway placement. An X-ray was then done to verify the position. The feeding tube was then advanced to the gastric position and subsequently confirmed by X-ray.¹³ Carbon dioxide was not detected in 52 out of 53 patients and all of them were verified to be in correct position by X-ray, so the technique was 100% specific. One placement out of the 53 was found to be in the trachea by X-ray and it was appropriately detected by color change thereby indicating no false negatives. To verify the sensitivity of this method, feeding tube was placed in trachea through ETT in 220 patients. In all 20 cases, CO_2 was detected thereby indicating 100% sensitivity. Thus, capnometry may be a safe and inexpensive method for confirming feeding tube placement. The study was conducted only in the mechanically ventilated patient, which may be a limitation.¹³

Control of Ventilation in Traumatic Brain Injury Patients

Aiming at "normocapnia" is practiced in the management of traumatic brain injury to avoid reduction in global cerebral blood flow and worsening of secondary brain injury due to vasoconstriction due to hyperventilation leading to hypocapnia. A capnograph can be effectively utilized for this purpose after intubation to guide ventilation parameters and thus prevent inadvertent hyperventilation.¹⁴

Capnography during Weaning from Mechanical Ventilation

This technology may also be applied during weaning process. Studies comparing postapneic end-tidal carbon dioxide pressure (PEtCO_2) with PaCO_2 before and after withdrawal of mechanical ventilation and showed good correlation ($r = 0.82$).¹⁵ In another prospective study, similar relationship was observed before and during weaning with continuous positive airway pressure ventilation, which detected important hypercapnic episodes.¹⁶ These studies did show a higher incidence of false positive, i.e., hypercapnic episodes leading to unnecessary blood sampling. Another useful concept advocated by Withington et al.¹⁷ in postcardiac surgery patients was to note the initial gradient between PaCO_2 and PEtCO_2 was established and then follow PEtCO_2 with necessary correction as a surrogate for PaCO_2 .

Postapneic end-tidal CO_2 pressure has been found to be useful as a predictor only in patients without significant parenchymal lung disease by Morley et al.¹⁸ which was in concordance with similar observation by Prause¹⁹ in prehospital emergency setting. This may be due to the fact that in the critically ill patient, alveolar dead space often changes and PEtCO_2 may not correlate with PaCO_2 and used as a substitute for arterial blood gas sampling.

CONCLUSION

Medical treatment has increasingly employed the detection of CO₂ for a variety of situations. Capnography is employed to monitor and evaluate respiratory functioning, it has enhanced the safety of mechanical ventilation and procedural sedation. Yet, there are many opportunities to glean additional useful information by looking beyond the simple end-tidal CO₂ value and taking the entire waveform into consideration. Based on the published studies, the value of EtCO₂ monitoring can be applied in variety of assessment in critically ill patients. These include conditions of impaired matching of ventilation and perfusion, such as pulmonary embolism and obstructive lung diseases; circulatory function, adequacy of chest compressions or fluid responsiveness in patients in shock.

REFERENCES

1. Boulos S, Schmidt GA. Capnography during critical illness. *Chest*. 2016;149(2):576-85.
2. Anderson CT, Breen PH. Carbon dioxide kinetics and capnography during critical care. *Crit Care*. 2000;4(4):207-15.
3. Yamanaka MK, Sue DY. Comparison of arterial-end-tidal PCO₂ difference and dead space/tidal volume ratio in respiratory failure. *Chest*. 1987;92(5):832-5.
4. Nagler J, Krauss B. Capnography: a valuable tool for airway management. *Emerg Med Clin N Am*. 2008;26(4):881-97.
5. Manara A, D'hoore W, Thys F. Capnography as a diagnostic tool for pulmonary embolism: a meta-analysis. *Ann Emerg Med*. 2013;62(6):584-91.
6. Moreira MM, Terzi RG, Carvalho CH, et al. Alveolar dead space and capnographic variables before and after thrombolysis in patients with acute pulmonary embolism. *Vasc Health Risk Manag*. 2009;5(1):9-12.
7. Strömberg NO, Gustafsson PM. Ventilation inhomogeneity assessed by nitrogen washout and ventilation-perfusion mismatch by capnography in stable and induced airway obstruction. *Pediatr Pulmonol*. 2000;29(2):94-102.
8. Brown RH, Brooker A, Wise RA, et al. Forced expiratory capnography and chronic obstructive pulmonary disease (COPD). *J Breath Res*. 2013;7(1):017108.
9. Lujan M, Canturri E, Moreno A, et al. Capnometry in spontaneously breathing patients: the influence of chronic obstructive pulmonary disease and expiration maneuvers. *Med Sci Monit*. 2008;14(9):CR485-92.
10. Paradis NA, Martin GB, Rivers EP, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA*. 1990;263(8):1106-13.
11. Monnet X, Bataille A, Magalhaes E, et al. End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. *Intensive Care Med*. 2013;39(1):93-100.
12. Krauss B, Hess DR. Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;50(2):172-81.
13. Araujo-Preza CE, Melhado ME, Gutierrez FJ, et al. Use of capnometry to verify feeding tube placement. *Crit Care Med*. 2002;30:2255-9.
14. Donald MJ, Paterson B. End tidal carbon dioxide monitoring in prehospital and retrieval medicine: a review. *Emerg Med J*. 2006;23(9):728-30.
15. Healey CJ, Fedullo AJ, Swinburne AJ, et al. Comparison of noninvasive measurements of carbon dioxide tension during withdrawal from mechanical ventilation. *Crit Care Med*. 1987;15(8):764-8.
16. Saura P, Blanch L, Lucangelo U, et al. Use of capnography to detect hypercapnic episodes during weaning from mechanical ventilation. *Intensive Care Med*. 1996;22:374-81.
17. Withington DE, Ramsay JG, Saoud AT, et al. Weaning from ventilation after cardiopulmonary bypass: evaluation of a noninvasive technique. *Can J Anaesth*. 1991;38(1):15-9.
18. Morley TF, Giaimo J, Maroszan E, et al. Use of capnography for assessment of the adequacy of alveolar ventilation during weaning from mechanical ventilation. *Am Rev Respir Dis*. 1993;148(2):339-44.
19. Prause G, Hetz H, Lauda P, et al. A comparison of the end-tidal CO₂ documented by capnometry and the arterial pCO₂ in emergency patients. *Resuscitation*. 1997;35(2):145-8.

Noninvasive Ventilation in the Perioperative Period

Vandana Agarwal

INTRODUCTION

Postoperative pulmonary complications (PPCs) have been reported in 5–10% of all surgical patients and 10–40% in patients undergoing abdominal surgery. Postoperative pulmonary complications can have significant adverse effect on perioperative outcomes. Fernandez-Perez et al. reported a 3% incidence of acute lung injury (ALI) in patients undergoing high-risk elective surgery. Acute lung injury was associated with increased length of intensive care unit (ICU) stay and significantly lower postoperative survival at 3 months and 1 year.¹ Based on the National Veterans Administration Surgical Quality Improvement Program database (n = 81,719) the most common postoperative complication was pneumonia (3.4%) and patients who developed postoperative respiratory failure (PRF) had significantly higher 30-day mortality.² Postoperative pulmonary outcome depends on preoperative respiratory condition and the degree of perioperative respiratory impairment.³ Postoperative respiratory failure requiring ventilation is not only associated with high morbidity and mortality, but also increases costs and length of hospital stay.

Noninvasive ventilation (NIV) can be instituted without an artificial airway, i.e., endotracheal tube or tracheostomy. Administration of NIV or continuous positive airway pressure (CPAP) after tracheal extubation in the early postoperative period not only reduces atelectasis and but improves pulmonary function.⁴ It can be used prophylactically to prevent occurrence of acute respiratory failure and therapeutically to treat respiratory failure.³

RISK FACTORS FOR POSTOPERATIVE RESPIRATORY FAILURE (BOX 1)

Effects of Anesthesia

Induction of anesthesia causes pathophysiological changes in the respiratory system such as reduction in muscle tone

leading to increase in retractile lung forces and development of atelectasis. Atelectasis causes a reduction in functional residual capacity, which may lead to impaired oxygenation, reduced lung compliance and development of lung injury.⁵ Atelectasis may also persist for a variable period in the postoperative phase despite initiation of spontaneous breathing and recovery from anesthesia. Diaphragmatic and respiratory muscle dysfunction can occur soon after surgery and last for 1–2 weeks in the postoperative period thus increasing the risk of PPCs. Good analgesia, patient's active involvement in postoperative pulmonary rehabilitation, and early mobilization all improve pulmonary function in the postoperative period.

Ventilator-induced Lung Injury

Conventionally, anesthesiologists ventilate patients with 10–12 mL/kg and without application of positive end-expiratory pressure (PEEP) during the intraoperative period. There is ample evidence of ventilator-induced lung injury (VILI) in critically ill patients with preexisting lung injury or pulmonary pathology. However, there's also increasing evidence of VILI in patients with normal or healthy lungs. Michelet et al. compared two ventilatory strategies in patients undergoing esophagectomy. One group was ventilated with 9 mL/kg tidal volume (TV) without PEEP both during one and two lung ventilation and the other group was ventilated with 9 mL/kg during two lung ventilation and 5 mL/kg with PEEP during one lung ventilation (OLV). They found improved oxygenation in OLV with PEEP both during and immediately after OLV with significantly lower inflammatory markers in patients with lower TV and PEEP and earlier extubation in the postoperative period.⁶ A multicenter, randomized controlled trial (RCT) compared protective lung ventilation with recruitment maneuvers with conventional ventilation in intermediate to high risk patients undergoing major abdominal surgery (IMPROVE study). They found 12% rate of PRF. Also in the protective ventilation group, there

Box 1: Risk factors for postoperative pulmonary complications**Patient factors**

- Age >65 years
- ASA ≥3
- Respiratory disease (COPD)
- History of respiratory infection within 1 month prior to surgery
- Obesity
- Obstructive sleep apnea
- Preoperative SpO₂ <96%
- History of congestive heart failure
- Poor functional status—(partial or total dependency)
- Active smoking
- Alcohol abuse
- Presence of preoperative sepsis
- Weight loss >10% in the last 6 months
- Preoperative anemia (<10 g/dL)

Surgical factors

- Surgical procedure:
 - Vascular
 - Thoracic
 - Upper abdominal
 - Neurosurgical
 - Head and neck
 - Cardiopulmonary bypass
- Emergency procedure
- Reexploration
- Surgery duration beyond 2 h
- Open procedure, e.g., laparotomy more than laparoscopy

Anesthetic factors

- Excess intraoperative fluids
- Conventional ventilation with high tidal volume and no PEEP
- Blood transfusion >4 units
- Intraoperative hypothermia
- Residual neuromuscular blockade
- Inappropriate ventilator settings
- Use of nasogastric tube
- Postoperative pain

COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure

was 69% reduction in the need for reintubation and NIV for PRF. This beneficial effect lasted as long as 7 days, which is the time period when the PPCs are most common.⁷ The PROVE investigators studied the impact of driving pressure (the difference between the plateau pressure and the level of PEEP on PPCs in patients undergoing protective ventilation during general anesthesia for surgery). They found that high-intraoperative driving pressure or any change in PEEP that resulted in increasing the driving pressure was significantly associated with more PPCs. Tidal volume was not found to be associated with PPCs.⁸ Recent meta-analysis including only RCTs in surgical and critically ill patients with healthy lungs suggest improved pulmonary outcomes in terms of pulmonary infection and acute respiratory distress syndrome (ARDS) incidence with protective mechanical ventilation strategy, but no effect on length of stay or mortality.⁹

Patient Factors

In addition to those listed in box 1, obese patients are at increased risk of PRF. The incidence of mortality secondary to PRF from the largest database of 13,000 patients undergoing bariatric surgery is about 11%.¹⁰ Patients with obstructive sleep apnea in addition to other comorbidities have a restrictive pulmonary disease with increased chest wall elastance and intra-abdominal pressure, which may promote lung atelectasis. The risk factors for postoperative respiratory depression are the severity of sleep apnea, increased sensitivity to systemic opioids, and sedatives. In addition, these patients should be monitored for a longer period in postanesthesia care unit or high dependency unit as the sleep pattern gets reestablished around the third or fourth postoperative day, which predisposes them to apnea

during the rapid eye movement sleep. It is recommended by the American Society of Anesthesiologists Task Force to prophylactically administer CPAP or NIV to these patients in the postoperative period.¹¹

Surgery

Surgery causes disruption of abdominal, thoracic, and diaphragmatic muscle forces. Surgical factors in addition to anesthesia-induced pathophysiological changes and postoperative pain lead to ventilation pump failure and/or ventilation perfusion mismatch thus causing respiratory failure.

Predicting Postoperative Respiratory Failure

Taking into consideration the incidence of PPCs and impact on outcomes, it seems prudent to identify patients at high risk for developing PRF and optimize and individualize the care during the perioperative period to prevent PRF. There are risk predictor models such as respiratory failure index and Score for Prediction of Postoperative Respiratory Complications.

Respiratory Failure Index (Tables 1 and 2)

It consists of patient-specific and surgery-specific factors. The type of surgery is weighed heavily followed by patient's nutrition, renal function, and functional capacity among other factors. Based on the score, patients are categorized into various risk class from 1–5 with increasing scores. This is derived and validated from a large prospective database from where patient characteristics and outcomes were obtained. There is slight over prediction of the risk in classes 3–5. Clinical

TABLE 1 Factors considered in respiratory failure index

Preoperative predictor	Point value
Types of surgery	
Abdominal aortic surgery	27
Thoracic surgery	21
Neurosurgery, upper abdominal and peripheral vascular surgery	14
Neck surgery	11
Emergency surgery	11
Albumin (<30 g/L)	9
Blood urea nitrogen (>30 mg/dL)	8
Partially or fully dependent functional status	7
History of COPD	6
Age (years)	
>70	6
60–69	4

COPD, chronic obstructive pulmonary disease

TABLE 2 Respiratory failure index predicted probability of postoperative respiratory failure based on points generated from patient- and surgery-specific variables

Class	Points	Predicted probability of PRF (%)
1	<10	0.5
2	11–19	2.2
3	20–27	5
4	28–40	11.6
5	>40	30.5

PRF, postoperative respiratory failure

application of this index should take into consideration the limitations. It can be used in men with high level of comorbidities. The index did not include pulmonary function test values and body mass index of the patients. A very broad definition of chronic obstructive pulmonary disease (COPD) was used, so there is possibility of underestimation of risk associated with severe COPD.²

Score for Prediction of Postoperative Respiratory Complications

Another predictive score derived and validated by Brueckmann et al. focused on reintubation in the early postoperative period, i.e., 3 days after surgery. It is highly predictive of postextubation respiratory failure. Reintubation within the 72 hours after surgery was found to be associated with increased risk (72-fold) of mortality. They identified five strong independent predictors of reintubation postoperatively such as: (i) ASA score of three or more, (ii) emergency procedures, (iii) type of surgery (vascular,

transplant, neurosurgery, thoracic, general surgery, and burns), (iv) a history of congestive heart failure, and (v) chronic pulmonary disease. Each variable was assigned a point value 3, 3, 2, 2, and 1, respectively. The probability of postoperative reintubation ranges from 0.12% with a score of 0–5.9% for scores of 7–11.¹²

BENEFIT OF NONINVASIVE VENTILATION IN THE PERIOPERATIVE PERIOD

Noninvasive ventilation or CPAP causes a reduction of atelectasis, thus improving lung volume, gas exchange, and alveolar minute ventilation. In addition to reducing the work of breathing, it reduces left ventricular afterload with increase in the cardiac output.

All these benefits are achieved without the need for endotracheal intubation, thus avoiding the risk associated with invasive mechanical ventilation.^{3,10} In a meta-analysis exploring the effects of NIV in the postoperative period, Glossop et al. found reduced risk of reintubation, pneumonia, and ICU and hospital length of stay when NIV was used postsurgery.¹³

ADMINISTERING NONINVASIVE VENTILATION IN A PATIENT UNDERGOING SURGERY

Noninvasive ventilation can be applied preoperatively, during induction of anesthesia and postoperatively. Postoperatively, NIV can be applied either prophylactically to prevent development of respiratory failure or therapeutically for treatment of respiratory failure.

Preoperative

- Obstructive sleep apnea: Patients who are already on home CPAP should continue the same prior to surgery
- Preoxygenation: The role of CPAP/NIV for preoxygenation is already established in critically ill patients. In patients at risk of hypoxemia, such as obese patients or patients with hypoxemia (ALI/ARDS for surgery), NIV is more effective in preventing desaturation during orotracheal intubation in comparison to conventional oxygenation.¹⁴

Postoperative

- Abdominal surgery: The incidence of hypoxemia postoperatively in patients undergoing upper abdominal surgery is as high as 30–50%. About 8% of these patients require invasive mechanical ventilation, thus increasing morbidity and mortality. Prophylactic application of CPAP after the extubation and in the postoperative period in patients undergoing abdominal surgery, improved lung volumes and gas exchange resulting in improved oxygenation. However, the rate of reintubation and

PPCs was similar to the conventional group. Therapeutic application of NIV was associated with reduced need for reintubation without any effect on mortality¹⁰

- **Thoracic and thoracoabdominal surgery:** The incidence of pulmonary complications leading to ALI or ARDS in patients undergoing lung resections for malignancy is about 4% with associated mortality of 64%. Perioperative prophylactic NIV in patients with forced expiratory volume in 1 second <70% administered 7 days preoperatively and 5 hours postoperatively for 72 hours after surgery improved oxygenation, spirometric values, and hospital length of stay.¹⁵ Similar improvement was seen in patients undergoing thoracoabdominal aortic aneurysmal repair in addition to reduced reintubation rate and reduced ICU stay¹⁶
- **Cardiac surgery:** Zarbock et al. compared standard treatment with prophylactic CPAP for at least 6 hours after extubation in patients undergoing cardiac surgery. Patients who receive CPAP had lower rate of hypoxemia, pneumonia and reintubation rate and readmission to the ICU¹⁷
- **Bariatric surgery:** In patients undergoing gastropasty, CPAP/NIV applied after surgery significantly improved arterial oxygenation, spirometric values, compared to oxygen therapy alone¹⁰
- **Solid organ transplantation:** Acute respiratory failure still is the most frequent cause of postoperative mortality following solid organ transplantation. In post solid organ (i.e., lung, liver, and kidney) transplant patients with hypoxemia, NIV when compared to supplemental oxygen improved oxygenation soon after application. These patients had few infective complications such as severe sepsis and septic shock, which can be attributed to avoidance of invasive mechanical ventilation. It was also associated with shorter length of ICU stay, but no difference in hospital outcome.¹⁸

PRECAUTIONS AND CONTRAINDICATIONS ASSOCIATED WITH NONINVASIVE VENTILATION (BOX 2)

When patients are administered NIV, they should be monitored for level of dyspnea, respiratory rate oxygen saturation, and in addition to washout of carbon dioxide in patients with hypercapnic respiratory failure. They should be observed for any signs of ventilator asynchrony, leaks, patient's comfort, gastric distension, dryness of eyes, and breakdown of facial skin at pressure points and necessary preventive measures should be taken for the same.³ When used therapeutically in postoperative patients, if the symptoms do not resolve, i.e., no improvement in oxygenation or respiratory rate or the level of consciousness deteriorates despite therapy within a stipulated time, especially with hemodynamic instability, one should

Box 2: Absolute and relative contraindications of noninvasive ventilation

Absolute contraindications

- Severe agitation or encephalopathy
- Inability to protect airway
- Facial trauma
- Patients with severe communicable airborne disease
- Cardiac or respiratory arrest
- Hemodynamic instability
- Immediate need for endotracheal intubation (except use of NIV for preoxygenation)
- Severe upper GI bleeding or hematemesis

Relative contraindications

- Uncooperative patient
- Slight decrease in level of consciousness
- Worsening respiratory failure

NIV, noninvasive ventilation; GI, gastrointestinal.

consider it as failure of NIV and progress to securing airway and establish invasive mechanical ventilation as in any critically ill patient.

Historically, NIV was contraindicated for upper-digestive anastomoses. The gastric inflation occurs at high insufflation pressures >25 cmH₂O. Risk of anastomotic breakdown secondary to high insufflation pressures may be decreased by using CPAP instead of bilevel ventilation (pressure support ventilation with PEEP). A large study of 1,000 patients addressed safety and efficacy of CPAP in preventing pulmonary complications following gastric bypass surgery. Only 15 had major anastomotic leaks and only two occurred in patients receiving CPAP.¹⁰ Presence of nasogastric tubes in postoperative patients may cause leaks and CPAP or NIV may be ineffective depending on the volume of leak. If the nasogastric tube is in place, it should be connected to draining bag rather than aspiration as gastric insufflation can be detected promptly.

CONCLUSION

Noninvasive ventilation or CPAP has a definite place in perioperative care of patients undergoing surgery. Identifying these patients preoperatively by the risk factors and modifying these factors are important to provide the best care with improved outcomes. Intraoperative use of protective ventilation strategy reduces the inflammation, incidence of infective complications, need for reintubation, and mechanical ventilation. Patients at high risk should be monitored in the high dependency unit or ICU for PRF. Judicious use of NIV/CPAP in the perioperative period, taking into consideration the limitations and concerns improves gas exchange, lung volumes, and reduces morbidity and length of stay.

REFERENCES

1. Fernandez-Perez ER, Sprung J, Alessa B, et al. Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case control study. *Thorax*. 2009;64(2):121-7.
2. Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Ann Surg*. 2000;232(2):242-53.
3. S Jaber, G Chanques, Jung B. Postoperative noninvasive ventilation. *Anesthesiology*. 2010;112(2):453-61.
4. Squadrone V, Coia M, Cerutti E, et al. Continuous positive airway pressure for the treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA*. 2005;293(5):589-95.
5. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology*. 2005;102(4):838-54.
6. Michelet P, D'Journo XB, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. *Anesthesiology*. 2006;105(5):911-9.
7. Futier E, Constantin JM, Paugam-Burtz C, et al. Atrial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369(5):428-37.
8. Neto AS, Hemmes SN, Barbas CS, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med*. 2016;4(4):272-80.
9. Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. *Crit Care*. 2014;18(2):211.
10. Chiumello D, Chevillard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. *Intensive Care Med*. 2011;37(6):918-29.
11. American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology*. 2014;120(2):268-86.
12. Brueckmann B, Uribe JV, Bateman BT, et al. Development and validation of a score for prediction of postoperative respiratory complications. *Anesthesiology*. 2013;118(6):1276-85.
13. Glossop AJ, Shephard N, Bryden DC, et al. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta-analysis. *Br J Anaesth*. 2012;109(3):305-14.
14. Hess DR. Noninvasive ventilation for acute respiratory failure. *Respir Care*. 2013;58(6):950-72.
15. Perrin C, Jullien V, Venissac N, et al. Prophylactic use of noninvasive ventilation in patients undergoing lung resectional surgery. *Respir Med*. 2007;101:1572-8.
16. Michelet P, D'Journo XB, Seinaye F, et al. Non-invasive ventilation for treatment of postoperative respiratory failure after oesophagectomy. *Br J Surg*. 2009;96(1):54-60.
17. Zarbock A, Mueller E, Netzer S, et al. Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from postoperative pulmonary complications: a prospective, randomized, controlled trial in 500 patients. *Chest*. 2009;135(5):1252-9.
18. Antonelli M, Conti G, Bui M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283(2):235-41.

Identifying Correctable Factors in Difficult Weaning

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INTRODUCTION

Weaning a patient from the ventilator is both an art and science. The experienced intensivist plays a major role in deciding as when to wean the patient off successfully. Moreover, spontaneous breathing trials (SBTs) done on daily basis can predict the ability to wean off successfully, though not sufficiently predictive. The pathophysiology of weaning failure is complex and includes both correctable and noncorrectable. This chapter deals with the correctable causes, their pathophysiology, assessment, and treatment strategies, so as to expedite weaning from mechanical ventilation.

EPIDEMIOLOGY AND DEFINITION OF WEANING FAILURE (TABLE 1)

Most of the patients in intensive care unit (ICU) can be weaned off easily but 20–30% patients are difficult to wean.¹ Successful weaning means that patient has been liberated from the mechanical ventilator support. The term “weaning failure” is applied to patients who have failed SBT or reintubated within 48 hours of extubation.¹ Extubation failure or difficult weaning is associated with prolonged ICU stay, increased mortality, and higher expenditure. Over the last 25 years, a thorough study of the literature reveals that patients who require prolonged ventilator support (≥ 21 days) accounts for approximately 6–10% of all patients treated

in ICU, however, consuming 37% of the ICU resources and costing >25 billion dollars/year.^{2,3}

Weaning should be a team decision rather than individual one. It must be started from the first day of ICU admission. Daily assessment for weaning should be incorporated into the patient’s treatment protocol because delay in extubation leads to increase in mortality.

Weaning is a stepwise process as depicted in flowchart 1. Skipping of any of the steps can lead to an adverse outcome. First step is assessing the patients for weaning followed by a SBT. If it is successful, patient is put on trial for extubation and reassessed for signs of reintubation or weaning failure.

Weaning is a complex process and its failure is always multifactorial. Various reversible/correctable and irreversible/noncorrectable causes have been defined for the weaning failure. Most common among them is cardio-respiratory destabilization along with metabolic and endocrine abnormalities. A thorough physical examination and investigations, particularly, blood markers and radiology are useful tools.

RESPIRATORY OR VENTILATION FACTORS

Acute respiratory failure is the most common cause for ICU admission and the most common indication for mechanical ventilator support.⁴ Planning for SBT or weaning process should be initiated when the underlying disease starts resolving and ventilator support requirement is minimal, i.e., inspiratory oxygen fraction (FiO_2) ≤ 0.5 , arterial oxygen tension (PaO_2)/ FiO_2 ratio >200 , and positive pressure requirement (PEEP) ≤ 8 cm H_2O .

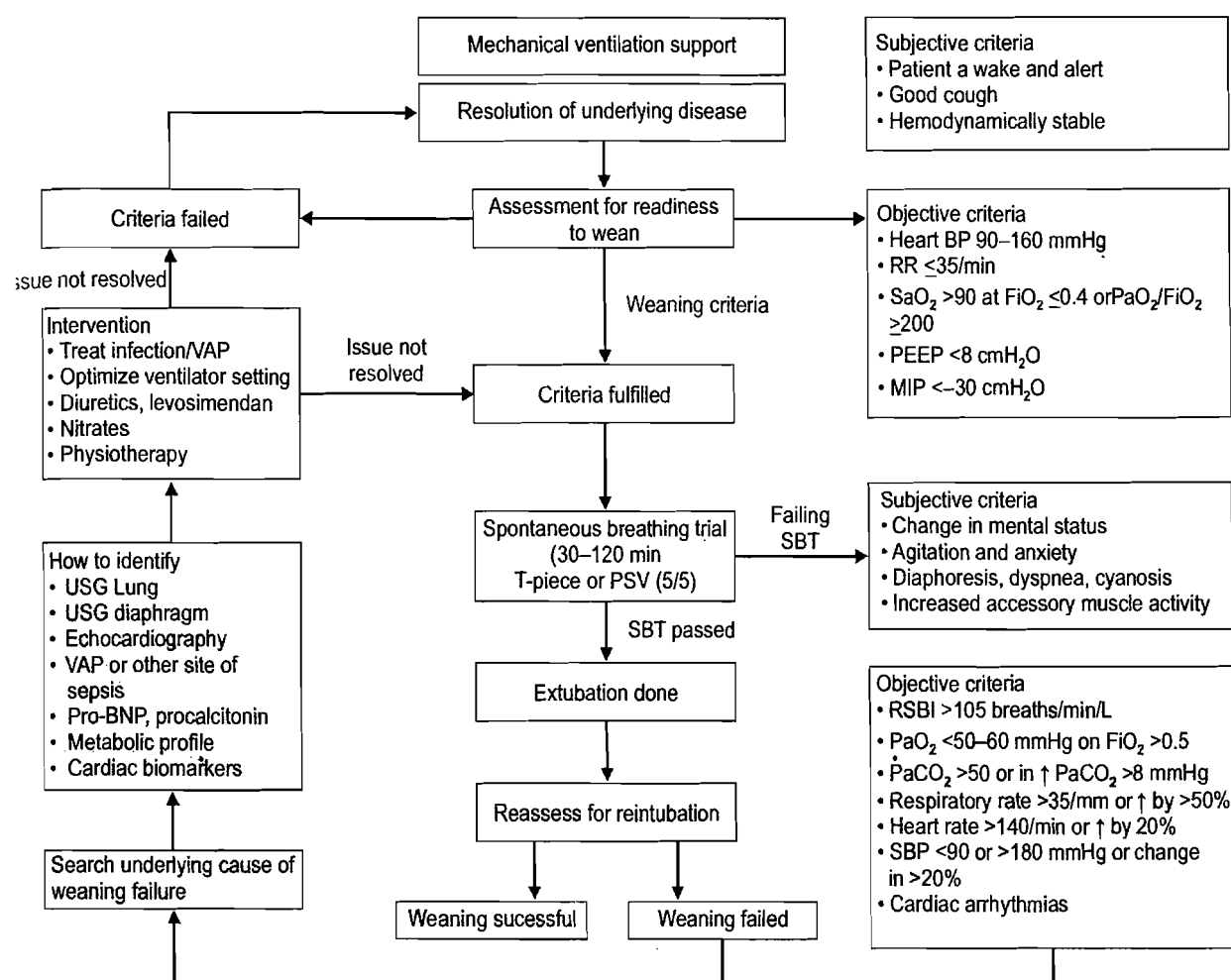
Weaning process depends upon the load on respiratory pump and capacity of respiratory muscles to handle it. Total work of breathing depends upon the resistance and elastance force. Increase in any one of the factors will lead to excessive work of breathing and respiratory failure.

Decrease in compliance is mostly because of atelectasis, pneumonia, pulmonary edema, and interstitial lung disease.

TABLE 1 Definition of various categories of weaning

Simple weaning	Patients who were extubated on the first attempt of weaning
Difficult weaning	Patients who fail first weaning trial or require up to 3 trials or as long as 7 days from the first SBT
Prolonged weaning	Patients who require >3 SBT or >7 days of weaning after first SBT

SBT, spontaneous breathing trial



PEEP, positive-end expiratory pressure; MIP, maximal inspiratory pressure; VAP, ventilator-associated pneumonia; USG, ultrasonography; Pro-BNP, pro-brain natriuretic peptide; RSBI, rapid shallow breathing index; SBT, spontaneous breathing trial; RR, respiratory rate.

FLOWCHART 1: Stepwise weaning process

Ventilator-associated pneumonia (VAP) is one of the common causes of poor compliance in ICU patients. Ventilator-associated pneumonia has a high-incidence rate of around 9–67% along with a high-mortality rate.⁵ Early identification and treatment of VAP can help in managing weaning failure. Total respiratory compliance is constituted by lungs and chest wall. The pathologies affecting the chest wall compliance like kyphoscoliosis, obesity, high-abdominal pressure, and pleural effusion can precipitate weaning failure.

Resistance in the upper airway is significantly associated with weaning failure. In fact, chronic obstructive pulmonary disease (COPD) is an independent risk factor for weaning failure.⁶ Airway resistance mainly depends upon diameter of airways, ventilator flow rate, and flow pattern and density of gas mixture. The most common affecting factor is diameter of airway lumen. Therefore, increased resistance is usually due to glottic edema, tracheal injury, tracheomalacia, bronchoconstriction, and due to endotracheal tube itself.⁷ Resistance to work of breathing may increase after extubation because of tracheal injury and edema.⁸ In such cases, patients may successfully pass the weaning assessment and SBT but fail extubation because of high resistance.

High resistance leads to expiratory flow limitation and air trapping. Air trapping, in turn, causes increase in intrinsic positive-end expiratory pressure (PEEPi). Intrinsic PEEP has negative effects in terms of increased work of breathing, ineffective triggering, and patient ventilator asynchrony.⁹ A patient needs to generate more negative pressure to overcome PEEPi, hence increasing the chance of weaning failure. So, understanding of basic lung physiology and its correlation with patient's clinical condition may help clinician to improve weaning success rates.

How to Identify

Measurement of compliance and resistance (Raw) can be done easily on ventilator. In fact, new ventilators are incorporated with equation that can calculate static compliance, dynamic compliance, and resistance. Static compliance = tidal volume (TV)/(P_{plat} – PEEP) and dynamic compliance = TV/(P_{peak} – PEEP). Normal value of static compliance is 60–100 mL/cmH₂O. Compliance can also be measured with pressure-volume curves. The compliance calculated with the above equation has both the components,

i.e., chest wall and lung. Esophageal pressure monitoring is required to differentiate chest wall and lung compliance. However, chest wall compliance does not alter over ICU stay. Therefore, changes in values are more important rather than static value. An intensivist should measure the baseline value of compliance at the time of admission and its trend while the patient is on mechanical ventilation in the following days. Other parameters like increase in FiO_2 requirement and radiological changes can also help in judging the cause of decreased compliance.

Airway resistance (R_{aw}) can be calculated on the ventilator with the following equation, keeping the flow rate constant. Estimated R_{aw} ($\text{cmH}_2\text{O/L/s}$) = $(\text{PIP} - P_{\text{plat}})/V$ (L/s). Normal airway resistance in intubated patient is 4–6 $\text{cmH}_2\text{O/L/s}$. Pressure-time and flow-time graphs provide qualitative assessment of resistance and expiratory flow limitation. Flow-time and flow-volume loops are highly informative about air trapping and dynamic hyperinflation. Simple bedside test of cuff leak can be used for suspected tracheal narrowing or edema. Cuff leak test is performed by deflating the endotracheal cuff completely and, thereby, checking for leakage of tidal volume. Direct visualization of airways with bronchoscope is gold standard for diagnosing tracheal stenosis, tracheomalacia, and airway narrowing.

Intervention

Treatment depends upon the underlying cause of weaning failure. Compliance can be improved by treating VAP, reducing interstitial edema, and draining pleural fluid and ascites. Resistive force can be decreased with optimization of ventilator settings and medical management. Chronic obstructive pulmonary disease patients can be weaned off with the help of noninvasive ventilation (NIV). Intrinsic PEEP can be countered by applying external PEEP to decrease work of breathing. Complications like tracheal stenosis and tracheomalacia may require airway stent and surgical treatment. In a study of 288 tracheostomized patients with difficult weaning, tracheal stenosis (>50%) was present in 14 patients. Patients were decannulated after surgical removal of granulation tissue.¹⁰

RESPIRATORY MUSCLE DYSFUNCTION

Neuromuscular dysfunction, as the etiology of weaning failure, still remains an underdiagnosed condition in any ICU setting. It can account for weaning failure in up to 62% of ICU cases.¹¹ Any patient who presents with or later on develops muscle weakness must be investigated for underlying cause because it puts a heavy impact on outcome. For example, patients of myasthenia gravis, motor neuron disease, and Guillain-Barre syndrome are difficult to wean off while snake bite, toxins, and electrolyte-related muscle weakness can be corrected easily.

A few patients in ICU may acquire peripheral neuromuscular dysfunction known as ICU-acquired weakness

(ICU-AW). Incidence of ICU-AW has been reported from 50–100%.¹² Major factors associated with ICU-AW are multiple organ dysfunction, severe inflammatory state, hyperglycemia, use of steroids, and irrational use of neuromuscular-blocking agents.^{13,14} Intensive care unit-AW can present as isolated neuropathy, myopathy or both. It is a diagnosis of exclusion and can be made bedside by muscle biopsy or neurophysiological conduction studies.

Patients on mechanical ventilator support may develop diaphragm weakness even without peripheral muscle weakness known as ventilator-induced diaphragm dysfunction (VIDD).^{15,16} Although clinical features and pathophysiology of ICU-AW and VIDD are overlapping, both the terms cannot be used interchangeably. Multiple theories have been given for VIDD, which include disuse atrophy and activation of proteolytic enzymes.¹⁵ Laghi et al. obtained the transdiaphragmatic pressure in mechanically ventilated patients by stimulating phrenic nerve and found a significant drop in pressure by 35% compared to that in healthy subjects.¹⁷ In such patients, increased workload after SBT cannot be handled by respiratory pump. Therefore, diaphragmatic weakness has been found to be an independent risk factor for weaning failure usually requiring tracheostomy.^{18,19}

How to Identify?

The diagnostic approach for diaphragmatic dysfunction needs electrophysiological and radiological investigations like maximal inspiratory pressure (MIP), magnetic stimulation of phrenic nerve, and bedside ultrasonography for assessing diaphragmatic contractions. Bilateral supramaximal magnetic twitch stimulation of the phrenic nerves has been considered as gold standard test for diaphragmatic function.²⁰ The test is invasive and is a research tool at present. The most widely used test in clinical practice is measurement of MIP, which is done by connecting a manometer to the tracheal tube. Lower limits for MIP in healthy subjects are –75 cmH_2O and –50 cmH_2O for men and women, respectively.²¹

Ultrasonographic assessment of diaphragm has become a regular investigation across the world. Because of easy availability and noninvasive nature, many ICU centers are using it as a screening tool for weaning assessment. On M-mode, diaphragmatic excursion should be <1 cm to be labeled as diaphragmatic weakness. Dinino et al. showed that diaphragm-thickening fraction (inspiratory minus expiratory thickness divided by expiratory thickness) of $\geq 30\%$ has a positive-predictive value of 91% for weaning success.¹⁶

Interventions

The treatment options for ICU-AW and VIDD are still lacking as most of the therapeutic interventional studies have been on animals. Data from human trials are not so promising. Current literature suggests that early shifting of ventilation from control mode to assist or support mode may decrease

the incidence because diaphragm inactivity triggers VIDD.²²⁻²⁴ Newer ventilatory modes like neurally adjusted ventilatory assist (NAVA) and proportional assist mode (PAV) seem suitable in these patients. These modes deliver support according to the patient's respiratory demand thereby protecting against over- or underassist support. People have used this strategy, especially in ICU-AW patients, and results are favorable. In a recent randomized controlled trial (RCT) in COPD patients who are difficult to wean, use of NAVA was associated with better patient ventilator synchrony and decreased hospital mortality as compared to conventional weaning mode.²⁵

A few studies have shown positive results with inspiratory muscle training exercise in difficult to wean patients.^{26,27} Device for muscle strengthening includes an adjustable spring loaded valve in which inspiratory threshold pressure can be titrated according to patient's effort. Another RCT has shown that 71% patients in strength training arm were weaned successfully against 47% in sham arm.²⁷ Other interventions like use of the antioxidants and tight glycemic control may be beneficial as shown by a few studies.^{28,29} Moderate hypercapnia exerts some protective effect on diaphragm. In addition, overuse of sedatives and neuromuscular agents should be avoided and calcium channel sensitizer, levosimendan may improve diaphragmatic contractility.³⁰

CARDIOVASCULAR FACTORS

Patients with cardiac conditions like valvular heart disease, cardiomyopathies, and ischemic heart disease are admitted in ICU with either primary or secondary problems. These patients usually have poor cardiopulmonary reserve and prone for developing weaning-induced pulmonary edema (Fig. 1). During SBT or after extubation, sudden shift from positive to negative pressure breathing puts extra load on heart.^{31,32} Negative pressure breathing increases the left ventricle-filling pressure either by increase in afterload or

decrease in left ventricle compliance. On the other side, right ventricle preload rises because of increased venous return, adrenergic tone, hypoxia and PEEPi. These complex cardiovascular interactions put extra burden on heart and incorporate the risk of weaning failure. Chronic obstructive pulmonary disease patients with left heart disease are at higher risk of weaning failure. Richard et al. found that COPD patients without underlying cardiac disease were associated with decreased left ventricular ejection fraction ($54\% \pm 12\%$ vs. $47\% \pm 13\%$) after mechanical ventilation versus spontaneous breathing.³³

How to Identify?

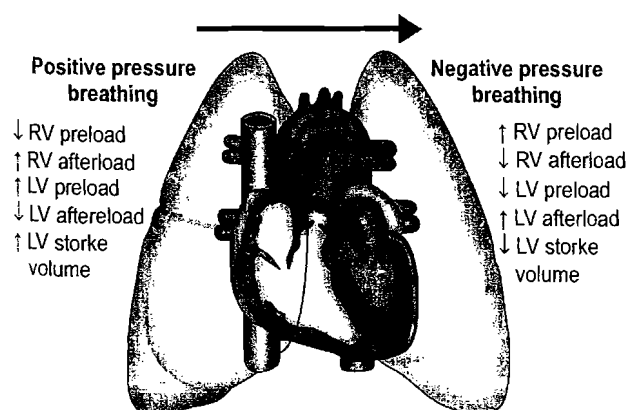
Invasive and noninvasive tests are available to detect underlying cardiac morbidity. The most preferred tests are noninvasive, which include electrocardiography, transthoracic cardiography and blood markers like B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Echocardiography has become a routine tool of investigation for cardiac performance status. Both the systolic and diastolic functions of heart can well be quantified with echocardiography that may help the intensivists to identify probable factors for weaning failure. Lamia et al. suggested that Doppler tissue imaging and transmitral flow variables could be used to detect weaning-induced elevation of left ventricle-filling pressure during SBT.³⁴

B-type natriuretic peptide is a hormone released by myocardium in response to overstretched or fluid overload state.^{35,36} Brain natriuretic peptide is found to be increased in SBT and extubation failure patient. Many studies have addressed the role of BNP in SBT failure patients. Zapata et al. concluded that BNP can predict weaning failure due to heart failure before an SBT.³⁶ The cutoff values were 263 ng/L for BNP ($p < 0.001$) and 1,343 ng/L for NT-proBNP. B-type natriuretic peptide was found to be a better marker than NT-proBNP in predicting chances of weaning failure. Chien et al. found that increased BNP after 2 hours of SBT also helps in predicting weaning failure.³⁵

Right heart catheterization is helpful to differentiate between cardiac and pulmonary causes of weaning failure. But because of invasive nature, its use is getting obsolete in most of the medical ICUs. Other markers like decreased mixed venous oxygen saturation and increased lactate are signs of poor cardiac performance status.³⁷

Interventions

It is important to analyze the cardiorespiratory mechanics during SBT. Weaning-induced pulmonary edema can be corrected by judicious use of diuretics, vasodilators, and inotropes. Loop diuretics can be used in patients suspected of pulmonary edema. Newer inotropes like levosimendan have shown positive results in decreasing ICU mortality.³⁸ Levosimendan is a calcium channel sensitizer used in



RV, right ventricular; LV, left ventricular; LA, left atrial; PCWP, pulmonary capillary wedge pressure.

FIG. 1: Cardiopulmonary interaction during mechanical ventilation

decompensated heart failure.³⁸ It has a beneficial effect over dobutamine and phosphodiesterase inhibitor. It does not increase myocardial oxygen demand, acts as vasodilator and improves diastolic function.^{39,40} In one trial, levosimendan was used in 12 patients who had poor ejection fraction and were difficult to wean. Seven patients were weaned within 51 hours of levosimendan infusion.⁴¹ Nitrates also have an excellent role in these situations because of their triple action. They decrease preload, afterload, and act as coronary artery dilator. In one study, nitrate infusion was tried in difficult to wean COPD patients. Twelve patients were included who failed at least 3 weaning trials and had systolic blood pressure >140 mmHg. Nitrate infusion was titrated to keep systolic pressure between 120 mmHg and 139 mmHg and seven patients were successfully extubated.⁴² Other therapies, like continuous positive airway pressure (CPAP) or NIV, can be used to counter the effects of negative pressure breathing. Continuous positive airway pressure therapy in cardiogenic pulmonary edema is a recommended choice of treatment.

NEUROCOGNITIVE FACTORS

Psychological Factors

Delirium and anxiety are common entities in ICU patients with incidence rate of 30–75%.⁴³ Sleep deprivation, drugs, sepsis, hypoxemia, prolonged immobilization, persistent pain, and use of sedative agents are independent risk factors for delirium.⁴⁴ All the above mentioned factors are easily identifiable and correctable also. Salam et al. found fourfold higher risk of failed extubation in patients of cognitive dysfunction.⁴⁵ Depression, anxiety, and sleep disturbances also hinder with successful weaning.^{46,47} Moreover, polysomnographic studies have shown poor quality of sleep and frequent arousal in ICU patients.⁴⁸ Ventilatory mode, pain, and ambient noise are risk factors for poor sleep.

Diagnosis and Correction

The confusion assessment method for ICU is a common screening tool for delirium in ICU patients.⁴⁹ Other tools and questionnaire are also available to assess cognitive function. Cautious use of sedatives and hypnotics along with assessment of cognitive function may help in improving weaning outcome. Midazolam has been considered as an independent risk factor for delirium. In a RCT, use of dexmedetomidine was found to reduce the incidence of delirium as compared to midazolam.⁵⁰ Sleep fragmentation and disturbances can be corrected by decreasing noise level, light and adequate pain management. Consultation with the psychiatrist and psychologist is helpful in cases of suspected depression, anxiety and cognitive dysfunction.

ELECTROLYTES, METABOLIC AND ENDOCRINE FACTORS

Fluid and electrolytes are commonly encountered problems in critically ill patients. Electrolyte abnormalities like hypokalemia, hypophosphatemia, and hypomagnesemia are all known to cause muscle weakness and various systemic dysfunctions, especially cardiac conduction abnormalities. Prevalence of various electrolyte imbalances could be as high as 50% especially hypomagnesemia and hypophosphatemia.⁵¹ These abnormalities must be excluded or corrected first before anticipating weaning failure. No large data is available to see the impact of individual electrolytes on weaning outcome prediction but many case reports in the literature reveal the impact of the individual electrolytes on weaning outcome and mortality. Metabolic disorders like acidosis and alkalosis have direct impact on respiratory drive and oxygen uptake at cellular level. These are usually iatrogenic in nature and can be corrected easily.

Hormones have an important role in stress. Cortisol and thyroid hormones have been studied and found to be associated with weaning failure. Role of corticosteroids is still controversial as an excess use can lead to myopathy. However, cortisol replacement is also necessary in deficit state. In a study, out of 93 patients of weaning difficulty, 70 were found to have adrenal insufficiency. In these patients, weaning duration decreased after using steroids.⁵² Similarly, thyroid disorders can delay extubation by causing muscle weakness or poor respiratory drive.⁵³ Replacing adequate amount of the deficit hormone can help in dealing difficult weaning patients.⁵⁴

Nutrition is one of the most concerned issues in critical patients. Intensive care unit patient are always at increased risk of malnourishment because of increased demand and poor enteral or parenteral nutrition. These undernourished patients are vulnerable to muscle wasting, weakness, increased duration of mechanical ventilation, and mortality.⁵⁵ Therefore, early enteral nutrition with an appropriate calorie intake is very essential in ICU. Obese or overweight patients have some better reserve in terms of nutrition but poor cardiorespiratory interaction. However, poor chest wall compliance and basal atelectasis may impact weaning outcomes in obese patients. Early intervention like NIV support in obese patients may prevent extubation failure.

CONCLUSION (TABLE 2)

As outlined, weaning failure is multicausative and a multidisciplinary approach along with a structured strategy is essential for prevention and early management. Still the area needs more research and trials as the knowledge in this arena is far from complete and the failure rates are far from negotiable figures.

TABLE 2 Summary of factors causing weaning failure and interventions support weaning

Pathophysiology	Cause	Assessment	Therapeutic interventions
Respiratory			
Increase resistance	<ul style="list-style-type: none"> • COPD • Asthma • Small diameter ET/tracheostomy tube • Mucus plug/blood clot • Glottic edema • Tracheal injury/stenosis • Tracheomalacia 	<ul style="list-style-type: none"> • Flow-time and pressure-time graph • Calculating resistance • Cuff leak test • Visualization by bronchoscopy 	<ul style="list-style-type: none"> • Applying external PEEP to counter internal PEEP and optimize ventilator settings • Bronchodilators • Adequate size ET/tracheostomy tube • Intravenous or oral steroid • Surgical removal of tracheal granulation tissue
Decrease compliance	<ul style="list-style-type: none"> • Interstitial lung disease • Ventilator-associated pneumonia • Cardiogenic/noncardiogenic pulmonary edema • Basal atelectasis • Pleural effusion, ascites, abdominal distension 	<ul style="list-style-type: none"> • Pressure-volume loop • Calculating compliance • Radiology (X-ray, CT thorax) • Lung ultrasonography 	<ul style="list-style-type: none"> • Recruitment maneuver • Low-tidal volume strategy • Adequate antibiotics use • Diuretics • Chest physiotherapy • Drainage of ascites and pleural fluid • Prokinetics and enema
Neuromuscular			
Diaphragm dysfunction	<ul style="list-style-type: none"> • ICU-acquired weakness (ICU-AW) • Ventilator-induced diaphragm dysfunction • Toxin (organophosphate poisoning) • Other neuromuscular disorders (myasthenia gravis, GBS, metabolic and infective) 	<ul style="list-style-type: none"> • Maximal inspiratory pressure • Phrenic nerve conduction velocity • Transdiaphragmatic pressure • Ultrasonographic assessment <ul style="list-style-type: none"> ◦ Diaphragmatic excursion ◦ Diaphragm-thickening fraction 	<ul style="list-style-type: none"> • Early use of assist/support mode • Inspiratory muscle training exercise • Antioxidants • Decrease use of sedation and neuromuscular blockers • Levosimendan and theophylline
Cardiac			
Increase cardiac workload	<ul style="list-style-type: none"> • Underlying cardiac disorder • Change in intrathoracic pressure 	<ul style="list-style-type: none"> • 12-lead ECG • Transthoracic echocardiography 	<ul style="list-style-type: none"> • Diuretics • Levosimendan, milrinone
Pulmonary edema	<ul style="list-style-type: none"> • Poor cardiopulmonary reserve 	<ul style="list-style-type: none"> • BNP or NT-proBNP • Cardiac biomarkers • ScVO₂, lactate • Right heart catheterization 	<ul style="list-style-type: none"> • Vasodilator-like nitrates • Beta-blocker in IHD • Noninvasive ventilation
Psychological factors			
Delirium Anxiety	<ul style="list-style-type: none"> • Sleep deprivation • Overuse of sedative agents • Prolonged immobilization • Sepsis 	<ul style="list-style-type: none"> • CAM-ICU 	<ul style="list-style-type: none"> • Adequate pain management • Cautious use of sedative agent • Dexmedetomidine • Haloperidol • Early immobilization
Metabolic factors			
Electrolyte abnormality	Hypokalemia Hypomagnesemia Hypophosphatemia	Electrolytes level	Early identification and correction of deficit factors
Cortisol deficiency	Hypothyroidism Hypoadrenalism	Cortisol level Thyroid profile	

COPD, chronic obstructive pulmonary disease; ET, endotracheal tube; PEEP, positive-end expiratory pressure; CT, computed tomography; ECG, electrocardiogram; IHD, ischemic heart disease; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; CAM-ICU, confusion assessment method for the intensive care unit.

REFERENCES

- Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29:1033-56.
- Carson S, Bach P. The epidemiology and costs of chronic critical illness. *Crit Care Clin*. 2002;18:461-76.
- Wagner DP. Economics of prolonged mechanical ventilation. *Am Rev Respir Dis*. 1989;140:14-8.
- Angus DC, Kelly MA, Schmitz RJ, et al. Committee on Manpower for Pulmonary and Critical Care Societies. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284:2762-70.

5. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867-903.
6. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1994;150:896-903.
7. Wilson AM, Gray DM, Thomas JG. Increases in endotracheal tube resistance are unpredictable relative to duration of intubation. *Chest*. 2009;136:1006-13.
8. Ishaaya AM, Nathan SD, Belman MJ. Work of breathing after extubation. *Chest*. 1995;107:204-9.
9. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1997;155:906-15.
10. Hagmeyer L, Oesterlee U, Tremli M, et al. Successful weaning and decannulation after interventional bronchoscopic recanalization of tracheal stenosis. *J Crit Care*. 2014;29:695:e9-14.
11. Spitzer AR, Giancarlo T, Maher L, et al. Neuromuscular causes of prolonged ventilator dependency. *Muscle Nerve*. 1992;15:682-6.
12. De Jonghe B, Sharshar T, Lefacheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288:2859-67.
13. Garnacho-Montero J, Madrazo-Osuna J, Garcia-Garmendia JL, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med*. 2001;27:1288-96.
14. Bercker S, Weber-Carstens S, Maria D, et al. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. *Crit Care Med*. 2005;33:711-5.
15. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. 2008;358:1327-35.
16. Jaber S, Petrof BJ, Jung B, Chanques G, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med*. 2011;183:364-71.
17. Laghi F, Cattapan SE, Jubran A, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? *Am J Respir Crit Care Med*. 2003;167:120-7.
18. De Jonghe B, Bastuji-Garin S, et al. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med*. 2004;30:1117-21.
19. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, et al. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med*. 2005;33:349-54.
20. Hermans G, Agten A, Testelmans D, et al. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. *Crit Care*. 2010;14:R127.
21. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis*. 1969;99:696-702.
22. DiNino E, Gartman EJ, Sethi JM, et al. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax*. 2014;69:423-7.
23. Sassoon C, Zhu E, Caiozzo V. Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med*. 2004;170:626-32.
24. Futier E, Constantin JM, Combaret L, et al. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. *Crit Care (London)*. 2008;12:R116.
25. T Kuo NY, Tu ML, Hung TY, et al. A randomized clinical trial of neurally adjusted ventilatory assist versus conventional weaning mode in patients with COPD and prolonged mechanical ventilation. *Int J Chron Obstruct Pulmon Dis*. 2016;11:945-51.
26. Martin AD, Davenport PD, Franceschi AC, et al. Use of inspiratory muscle strength training to facilitate ventilator weaning: a series of 10 consecutive patients. *Chest*. 2002;122:192-6.
27. Martin AD, Smith BK, Davenport PD, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care*. 2011;15:R84.
28. Travalline JM, Sudarshan S, Roy BG, et al. Effect of N-acetylcysteine on human diaphragm strength and fatigability. *Am J Respir Crit Care Med*. 1997;156:1567-71.
29. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-97.
30. Van Hees HW, Dekhuijzen PN, et al. Levosimendan enhances force generation of diaphragm muscle from patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179:41-7.
31. Lamia B, Monnet X, Teboul JL. Weaning-induced Cardiac Dysfunction. In: Vincent JL (Eds). *Yearbook of Intensive Care and Emergency Medicine*, 1st edition. Heidelberg: Springer; 2005. Pp. 239-45.
32. Frazier SK, Stone KS, Schertel ER, et al. A comparison of hemodynamic changes during the transition from mechanical ventilation to T-piece, pressure support, and continuous positive airway pressure in canines. *Biol Res Nurs*. 2000;4:253-64.
33. Richard C, Teboul JL, Archambaud F, et al. Left ventricular function during weaning of patients with chronic obstructive pulmonary disease. *Intensive Care Med*. 1994;20:181-6.
34. Lamia B, Maizel J, Ochagavia A, et al. Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. *Crit Care Med*. 2009;37:1696-701.
35. Chien JY, Lin MS, Huang YC, et al. Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. *Crit Care Med*. 2008;36:1421-6.
36. Zapata L, Vera P, Roglan A, Gich I, et al. B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. *Intensive Care Med*. 2011;37:477-85.
37. Laghi F. Weaning from mechanical ventilation. In: Gabrielli A, Layon AJ, Yu M (Eds). *Civetta, Taylor and Kirby's Critical Care*. Pennsylvania: Lippincott Williams & Wilkins; 2009. pp. 1991-2028.
38. Landoni G, Mizzi A, Biondi-Zoccai G, et al. Levosimendan reduces mortality in critically ill patients. A meta-analysis of randomized controlled studies. *Minerva Anestesiologica*. 2010;76:276-86.
39. Givertz MM, Andreou C, Conrad CH, et al. Direct myocardial effects of levosimendan in humans with left ventricular dysfunction: alteration of force-frequency and relaxation-frequency relationships. *Circulation*. 2007;115:1218-24.
40. Deschodt-Arsac V, Calmettes G, Raffard G, et al. Absence of mitochondrial activation during levosimendan inotropic action in perfused paced guinea pig hearts as demonstrated by modular control analysis. *Am J Physiol Regul Integr Comp Physiol*. 2010;299:R786-92.
41. Sterba M, Banerjee A, Mudaliar Y. Prospective observational study of levosimendan and weaning of difficult-to-wean ventilator dependent intensive care patients. *Crit Care Resusc*. 2008;10:182-6.
42. Routsis C, Stanopoulos I, Zakynthinos E, et al. Nitroglycerin can facilitate weaning of difficult-to-wean chronic obstructive pulmonary disease patients: a prospective interventional non-randomized study. *Crit Care*. 2010;14:R204.
43. Chlan LL. Description of anxiety levels by individual differences and clinical factors in patients receiving mechanical ventilatory support. *Heart Lung*. 2003;32:275-82.
44. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340:669-76.
45. Salam A, Tilluckdharry L, Amoateng-Adjepong Y, et al. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med*. 2004;30:1334-9.
46. Rothenhäusler HB, Ehrentraut S, von Degenfeld G, et al. Treatment of depression with methylphenidate in patients difficult to wean from mechanical ventilation in the intensive care unit. *J Clin Psychiatry*. 2000;61:750-5.
47. Jubran A, Lawm G, Kelly J, Duffner LA, et al. Depressive disorders during weaning from prolonged mechanical ventilation. *Intensive Care Med*. 2010;36:828-35.
48. Cooper AB, Thomsley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. *Chest*. 2000;117:809-18.
49. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286:2703-10.
50. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301:489-99.
51. Besunder JB, Smith PG. Toxic effects of electrolyte and trace mineral administration in the intensive care unit. *Crit Care Clin*. 1991;7:659-93.
52. Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. *Am J Respir Crit Care Med*. 2006;173:276-80.
53. Martinez FJ, Bermudez-Gomez M, Celli BR. Hypothyroidism: A reversible cause of diaphragmatic dysfunction. *Chest*. 1989;96:1059-63.
54. Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. *Chest*. 2004;126:1307-12.
55. Dempsey DT, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am J Clin Nutr*. 1988;47:352-6.

Driving Pressure in Acute Respiratory Distress Syndrome: Is It Relevant?

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a common cause of acute respiratory failure in intensive care unit. It is a disorder, where there is pulmonary capillary endothelial damage causing noncardiogenic pulmonary edema leading to refractory hypoxia. The management of ARDS has changed considerably in the past decade with improved survival¹ but still has a mortality rate of >40%. Almost half of mortality is due to sepsis with multiorgan failure followed by refractory hypoxia (16%), cardiac failure or arrhythmias (15%), neurological failure (10%), and other causes (8%).² mortality increases with increasing age and increasing organ failures. So, the primary goal in ARDS management would be prevention of sepsis and organ failures. Mechanical ventilation itself can lead to lung damage and other distant organ damage—ventilation induced lung injury (VILI).³ Different strategies have been developed to limit VILI and further organ dysfunction.

VENTILATING ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS—WHAT WE KNOW AND EMERGING CONCERNS

Mechanical ventilation is commonly initiated for respiratory failure due to ARDS. There is innumerable evidence available to show higher tidal volume (Vt) ventilation leads to lung injury.^{4,5} Ventilating patients with ARDS have shown paradigm shift from traditional high Vt to low tidal ventilation 6 mL/kg predicted body weight. “Protective lung ventilation” strategy, i.e., combination of low Vt ventilation, low plateau pressure (P_{plat}) (<28–30 cmH₂O), and higher positive end-expiratory pressure (PEEP), has improved survival.^{5–7} This strategy minimizes the lung injury by limiting the end-inspiratory pressure (lung stress—force applied to lung tissue) reducing alveolar over distension and lung strain (deformation occurring in lung tissue). It also prevents frequent opening and closing of alveolus (atelectrauma).³

Protective lung ventilation with low Vt is safe and beneficial even in patients without ARDS and have also shown to prevent progression to ARDS.^{8,9}

However, low tidal ventilation leads to more atelectasis, hypoxia and requirement of higher PEEP. Ventilating ARDS patients with higher PEEP is still a debate since no survival benefit has been shown except in patients with severe ARDS.¹⁰ Setting an optimal PEEP to prevent overdistension and derecruitment is not easy, and several methods like using lung compliance, transpulmonary pressure, decremental PEEP trial following recruitment, and fraction of inspired oxygen (FiO₂)-PEEP tables have been tried with varying results.

CRITICAL CONCERNS ON LOW TIDAL VENTILATION STRATEGY

The lung in ARDS patients is heterogeneous with mixture of consolidated, partially collapsed, and normal alveolar tissue. The lung volume is small rather stiff, i.e., “the baby lung” concept introduced by Gattinoni and Pesenti¹¹ showed that the volume of lungs available for ventilation is small and it is difficult to predict the volume of baby lung. Mechanical ventilation with lung protective strategy as a whole has been proved beneficial but the impact of individual components is unknown.

Lung volumes and capacity correlate with height of the patient and in turn to predicted body weight.¹² Reducing Vt according to predicted body weight has shown to reduce VILI, improved survival, and more ventilator free days, but not in all patients.^{13,14} As the volume of lungs available for ventilation is not uniformly reduced among patients,¹¹ ventilating with same low Vt based on predicted body weight will produce alveolar overdistension in some patients, and hence, leading to different lung stress and strain among them.¹⁵

So, reducing Vt further to 3–4 mL/kg predicted body weight may prevent alveolar overdistension and reduce VILI but raises serious concern of carbon dioxide elimination.

Ultraproductive ventilation strategy with V_t of 3 mL/kg ideal body weight with extracorporeal carbon dioxide removal was found to be safe and effective but without any survival advantage compared to lung protective ventilation with V_t of 6 mL/kg.¹⁶ In the above study, V_t was adjusted according to body weight rather than compliance, so considering only V_t rather than amount of available functional lung size did not offer any further advantage.

Plateau pressure may vary according to chest wall compliance like in obese patients, so titrating V_t according to P_{plat} may lead to hypoventilation. Esophageal pressure measurement that is used to measure transpulmonary pressure is not universally available and has many limitations.^{17,18} Terragni et al. showed that low tidal ventilation also led to tidal hyperinflation in ARDS patients that may be attributed to high P_{plat} .¹³ Whether higher P_{plat} is an indicator of severity of disease or lung injury is unclear. Setting and titrating PEEP are controversial since both lower and higher PEEP have no survival benefit. Alteration of one component has an impact on each other and is closely inter-related. When there is overdistension, the airway pressure increases and compliance decreases and vice versa. So, there is a close relationship between compliance of respiratory system and airway pressure with the volume of baby lung. So, optimizing V_t to compliance or airway pressure rather predicted body weight may be better predictor of lung stress and strain.

DRIVING PRESSURE—THE PHYSIOLOGICAL BASIS AND CLINICAL APPLICATION

Driving pressure (ΔP) is the ratio of V_t to static compliance of respiratory system.

$\Delta P = \text{Tidal volume (} V_t \text{)} / \text{Respiratory system compliance (} C_{rs} \text{)}$

Clinically, ΔP is the difference between alveolar P_{plat} and PEEP, i.e.,

$$\begin{aligned}\Delta P &= P_{plat} - PEEP \\ P_{plat} - PEEP &= V_t / C_{rs} \\ (C_{rs} &= V_t / P_{plat} - PEEP)\end{aligned}$$

Both PEEP and V_t are independent variables and can be altered by physician, but P_{plat} and compliance are dependent variables. So, any change in independent variable affects the dependent variable.

When increasing the V_t or PEEP, if there is recruitment then ΔP will decrease and compliance increases, but if there is overdistension then worsening of compliance and increase in ΔP occurs (Fig. 1). ΔP and compliance are inter-related. ΔP may be defined better as the amount of cyclical alveolar deformation imposed on ventilating lung units.

When we measure compliance (C_{rs}), we are actually measuring the compliance of thorax as a whole, and lungs are just a part of it. Hence, if we need to know the distending pressure of lungs alone, we need to measure transpulmonary pressure (alveolar – pleural pressure/esophageal pressure) which is clinically not feasible.

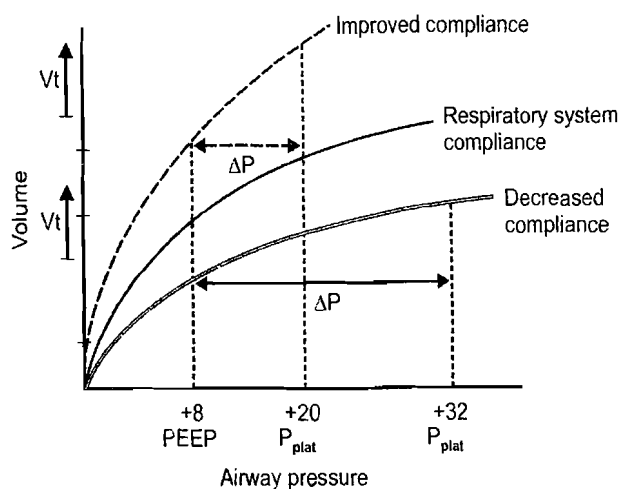
Another easy bedside surrogate method to know the change in compliance is the stress index¹⁹ (Fig. 2). It is noted from the terminal part of pressure time curve of volume controlled breath with constant flow in a well-relaxed or paralyzed patient. When the terminal part of pressure time curve is concave downward, it represents good compliance (stress index <1); concave upwards it represents poor compliance (stress index >1); flat represents normal compliance (stress index = 1). To know the real stress on lung, we need to measure transpulmonary stress index and it is clinically challenging. Transpulmonary stress index can be substituted by airway pressure stress since there is good correlation between them.^{20,21}

Airway stress index is a simple bedside tool to track respiratory compliance to ventilator adjustments and hence used to predict lung injury during ventilation.²² Both V_t and PEEP can be titrated to stress index to limit lung injury.²³⁻²⁵ Stress index reflects the respiratory compliance which in turn have impact on ΔP ($C_{rs} = V_t / P_{plat} - PEEP$), so, low-stress index will have low ΔP and vice versa. Airway ΔP has shown to have close relation with transpulmonary ΔP and reflect the lung stress.²⁶ So, ΔP is an indicator of lung stress as stress index. ΔP is easy to measure, more objective and easy to keep a trend but patient should be relaxed and without any active breathing.

DRIVING PRESSURE—A NEW TARGET FOR VENTILATION OF ARDS PATIENTS

Ventilator induced lung injury is due to lung stress and strain, which is proportional to the pressure applied to the lung. As lung stress and strain is difficult to measure in clinical practice, airway ΔP can be used to predict lung injury. Higher the ΔP greater the lung injury.²⁶

Recently, Amato et al.²⁷ showed in their multilevel mediation analysis of 3,562 ARDS patients from nine



P_{plat} , plateau pressure; PEEP, positive end-expiratory pressure; ΔP , driving pressure; V_t , tidal volume.

FIG. 1: Compliance and driving pressure

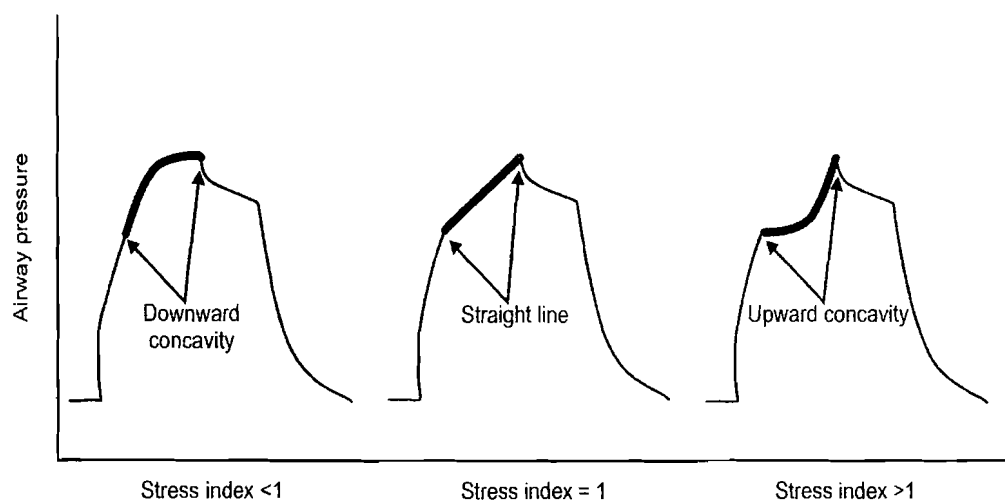


FIG. 2: Stress index

previous randomized controlled trials that ΔP is a better predictor of ARDS outcome. The independent variables associated with improved outcome were ΔP , partial arterial pressure of oxygen/ FiO_2 ratio at entry, pH at entry, risk of death (Acute Physiology and Chronic Health Evaluation and Simplified Acute Physiology Score). The authors did multiple resampling considering subgroups of patients with matched mean levels for one variable but different mean level for another ranking variable and found that increased ΔP was associated with increased mortality (Table 1). The reduction in V_t or increase in PEEP was found beneficial only if associated with decrease in ΔP . The key message from this analysis is ΔP is an independent predictor of survival in patients with ARDS.

A few other studies have also shown the importance of ΔP in ARDS patient survival. In an animal study where ARDS was artificially induced, authors used varying combinations of V_t and PEEP to yield different transpulmonary ΔP found that combination of low V_t and PEEP, yielding low transpulmonary ΔP and P_{plat} had minimal lung injury. Chiumello et al.²⁶

divided patients into two groups of PEEP 5 and 15 cmH_2O and performed recruitment maneuver to all patients to keep lungs open and more homogeneous. Lung stress (cmH_2O) was calculated accordingly as:

Lung stress = (airway pressure plateau – atmospheric pressure) – (esophageal pressure plateau – esophageal atmospheric pressure).

Patients were analyzed in two groups, $\Delta P < 15 \text{ cmH}_2\text{O}$ and $> 15 \text{ cmH}_2\text{O}$. Lung stress $> 26 \text{ cmH}_2\text{O}$ was considered significant. Patients with higher ΔP had higher lung stress in both groups and airway ΔP was accurate at detecting lung stress.

Low ΔP is associated with improved survival, but achieving lower ΔP may be a challenge. In patients with ARDS with good recruitable lung after recruitment maneuver and appropriate PEEP the functional lung size increases and transpulmonary pressure gets evenly distributed leading to better compliance and lower ΔP . Borges et al. illustrated improved compliance, oxygenation with lower ΔP after recruitment maneuver and appropriate PEEP.

CONCLUSION

Lungs in patients with ARDS are heterogeneous and small. Compliance of lungs reflects the severity of disease and functional size of lung. Severe the ARDS, more is the VILI because of more heterogeneous lung and unpredictable functional lung volume. Higher ΔP is associated with increased lung stress. Analysis by Amato et al.²⁷ is a retrospective observational study, analyzed from heterogeneous group of ARDS patients and ΔP is a postrandomization variable. Further prospective randomized studies are needed to confirm the above results. As higher ΔP is associated with increased lung stress, ventilation parameters should be set to have minimal ΔP . Tidal volume should be scaled to compliance (ΔP) rather predicted body weight and further reduction can be done to meet target ΔP .

TABLE 1 Subgroups with matched mean of one variable and different mean of another variable and combined population

Combination of variables		Outcome
Fixed PEEP	Increasing ΔP	Increased mortality
Fixed PEEP	Decreasing ΔP	Decreased mortality
Increased PEEP	Fixed ΔP	No effect on mortality
Fixed plateau pressure	Increased/decreased ΔP	Increased/decreased mortality
In combined population		
Decreased V_t , increased PEEP	Decreasing ΔP	Decreased mortality

V_t , tidal volume; PEEP, positive end-expiratory pressure; ΔP , driving pressure

Lung recruitment followed by appropriate PEEP in patients with recruitable lung can be tried to achieve lowest possible ΔP . But whether reducing ΔP using recruitment maneuver and high PEEP would improve outcome is unclear. Whether to alter ventilation parameters when there is high ΔP and low P_{plat} and vice versa needs further evaluation. So, ΔP is an emerging concept that optimizes ventilation of available functional lung volume in ARDS patients. At this point of time, the clinical utility and safety of ΔP need confirmation from further studies.

REFERENCES

- Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med*. 2009;179(3):220-7.
- Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? *Eur Respir J*. 1997;10(6):1297-300.
- Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-36.
- Amato MB, Barbas GS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-54.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-8.
- Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. *N Engl J Med*. 2007;357(11):1113-20.
- Villar J, Kacmarek RM, Perez-Mendez L, et al. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med*. 2006;34(5):1311-8.
- Martin-Loeches I, de Haro C, Dellinger RP, et al. Effectiveness of an inspiratory pressure-limited approach to mechanical ventilation in septic patients. *Eur Respir J*. 2013;41(1):157-64.
- Fuller BM, Mohr NM, Drewry AM, et al. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: a systematic review. *Crit Care*. 2013;17(1):R11.
- Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-73.
- Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med*. 2005;31(6):776-84.
- Ibanez J, Raurich JM. Normal values of functional residual capacity in the sitting and supine positions. *Intensive Care Med*. 1982;8(4):173-7.
- Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2007;175(2):160-6.
- Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med*. 2005;33(1):1-6.
- Chiumello D, Carlesso E, Cadringer P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2008;178(4):346-55.
- Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈ 3 ml/kg) combined with extracorporeal CO₂ removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5):847-56.
- Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008;359(20):2095-104.
- Benditt JO. Esophageal and gastric pressure measurements. *Respir Care*. 2005;50(1):68-75.
- Grasso S, Terragni P, Mascia L, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med*. 2004;32(4):1018-27.
- Pan C, Chen L, Zhang Y-H, et al. Physiological Correlation of Airway Pressure and Transpulmonary Pressure Stress Index on Respiratory Mechanics in Acute Respiratory Failure. *Chin Med J*. 2016;129(14):1652-7.
- Chiumello D, Carlesso E, Miletto C, et al. Stress Index: Is the Airway Pressure a Good Surrogate of the Transpulmonary Pressure? *Am J Respir Crit Care Med*. 2010;181:1.
- Terragni PP, Filippini C, Slutsky A, et al. Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. *Anesthesiology*. 2013;119(4):880-9.
- Ferrando C, Suárez-Sipmann F, Gutierrez A, et al. "Adjusting tidal volume to stress index in an open lung condition optimizes ventilation and prevents overdistension in an experimental model of lung injury and reduced chest wall compliance." *Crit Care*. 2015;19:9.
- Miñana A, Ferrando C, Arocas B, et al. Matching tidal volume to stress index in an open lung condition optimizes ventilation and prevents VILI in an experimental model of lung injury and intra-abdominal hypertension: 5AP1-3. *Eur J Anaesthesiol*. 2014;31:76-7.
- Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176(8):761-7.
- Chiumello D, Carlesso E, Brioni M, et al. Airway driving pressure and lung stress in ARDS patients. *Crit Care*. 2016;20:276.
- Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-55.

Prone Ventilation in Acute Respiratory Distress Syndrome: Why, When, and for How Long?

Rajesh Chawla, Aakanksha Chawla

INTRODUCTION

Majority of patients with severe respiratory failure need invasive mechanical ventilation and they are traditionally ventilated in the supine position. When oxygenation goals are not met in a patient of acute respiratory distress syndrome (ARDS) in supine position then these patients are ventilated successfully in prone position. Efficacy of prone position in improving hypoxemia has been shown in multiple studies.¹⁻⁶ Recent studies have shown that it improves survival as well.⁷⁻¹⁴

DEFINITION

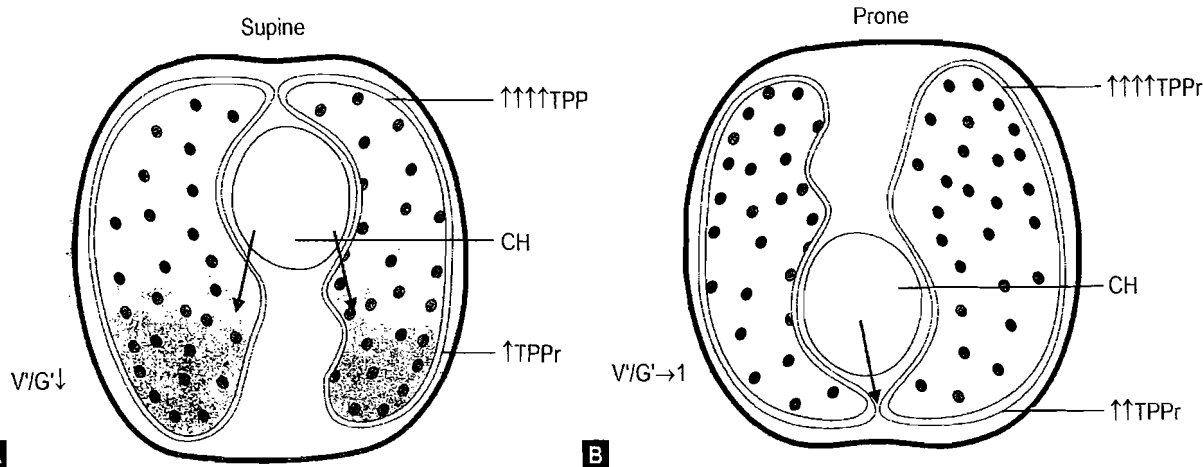
Prone ventilation is the delivery of traditional mode of ventilation in prone position. So, patient can be ventilated in prone position using volume control or pressure preset ventilation or other modes (Fig. 1). Prone ventilation can also be used with high frequency ventilation.



FIG. 1: Prone positioning

PHYSIOLOGICAL ADVANTAGES OF PRONE VENTILATION

- In supine position, dependent lung is partially collapsed. The heart compresses the medial and posterior portion of lung and, at the same time, diaphragm compresses the posterior and inferior part of the lung parenchyma. Abdominal contents displace the diaphragm upwards which is further aggravated by the effect of sedation, paralysis, and increased intra-abdominal pressure. So, this aggravates the dependent lung collapse and worsens hypoxemia in supine position. During prone ventilation, the heart lies on the sternum and it relieves the compression of the medial and posterior portion of the lung parenchyma and, at the same time, the diaphragm is displaced caudally which will decrease compressive effect on the medial and inferior lung^{15,16}
- Improved ventilation perfusion: In supine position, both blood flow and alveolar collapse are maximum at the dependent dorsal portion of the lung which results in ventilation perfusion mismatch as the ventilation is much less and perfusion is maximum in this region. Ventilation perfusion mismatch improves in prone position because the dorsal region continues to receive the maximum blood flow and the alveoli reopen and the ventral region or the newly dependent region continues to get less blood flow and the alveoli collapse. All of these result in improvements in ventilation perfusion match
- During prone ventilation, there is improvement in lung recruitment and hypoxemia which results in decrease in hypoxic pulmonary vasoconstriction. This increases right ventricular preload and leads to decrease in right ventricular afterload and pulmonary vascular resistance which increases cardiac output^{17,18}
- Decreased gradient between ventral and dorsal transpulmonary pressure: Transpulmonary pressure (Ptp) is defined as the difference of airway pressure and pleural



TPPr, transpulmonary pressure; CH, cardiac; V/Q, ventilation/perfusion; TPP, transpulmonary pressure.

FIG. 2: Effect of proning on transpulmonary pressure and improved ventilation/perfusion mismatch

pressure (Ppl). When patient lies in supine position, the dorsal Ppl is more than the ventral Ppl. Ventral Ptp is more than the dorsal Ptp which causes more expansion of ventral alveoli in supine position. This effect gets augmented in ARDS patient which will result in hyperinflation of ventral area. In prone position, the Ppl gradient is decreased between ventral and dorsal regions which makes ventilation more homogenous which will not only recruit alveoli but also prevent ventilator-induced lung injury (Fig. 2). This improvement in prone position is maintained in supine position.¹⁹⁻²³

- There is better drainage of pulmonary secretions in prone positions and the delivery of aerosol is also improved in prone positioning which results in better ventilation.

WHEN TO PRONE?

Lung protective strategy is the initial ventilation strategy in most patients with ARDS. The patient is ventilated in either volume or pressure control mode. Tidal volume is maintained at 6 mL/kg of ideal body weight and end-inspiratory pressure below 30 cmH₂O at all times. Patient with severe ARDS who do not improve with the use of this kind of ventilatory strategy, prone ventilation should be tried to improve oxygenation and provide safe ventilation. It is also used for a patient waiting for extracorporeal membrane oxygenation (ECMO). Refractory hypoxemia and severity of ARDS that warrants prone ventilation has been variably defined as PaO₂:FiO₂ (partial pressure arterial oxygen/fraction of inspired oxygen ratio or P/F ratio) of ≤100 mmHg and a PaO₂ ≤60 mmHg despite appropriate vent strategy on FiO₂ of 1.

EVIDENCE FOR EFFICACY OF PRONE VENTILATION

Five large randomized controlled trials (RCTs) and a few small studies have tested the role of prone positioning in improving patient survival.⁶ Earlier trials had shown improvement in

oxygenation with prone position but did not show mortality benefit.¹⁻⁶ These trials have consistently demonstrated that prone ventilation improves oxygenation which is defined as 10 mmHg increase in PaO₂, resulting in reduction in the FiO₂. It is interesting to note that patients whose oxygenation improves during prone ventilation continue to have improved oxygenation for long time after patient is turned into the supine position. The improvement is seen each time the patient is put in prone position. Many patients will show this improvement in first hour but some do show it later.

There are some factors which predict improved oxygenation during prone ventilation. Patients who have diffuse pulmonary edema and dependent alveolar collapse as compared to consolidation are more likely to improve their oxygenation during prone ventilation. Similarly, patients who have an extrapulmonary cause as compared to pulmonary cause for their ARDS are more likely to show improvement in their oxygenation.²⁴ Patients with elevated intra-abdominal pressure increase their PaO₂ during prone ventilation as compared to patient with normal intra-abdominal pressure.^{25,26} Patients whose chest wall compliance decreases in prone position are more likely to improve their PaO₂.²⁶

Generally, for a long time in patients of ARDS, no significant mortality benefit was demonstrated with prone positioning in various randomized trials and meta-analyses.⁷⁻¹⁴ Some meta-analyses had reported mortality benefits in subset of severe ARDS whose P/F ratio was <100 mmHg.^{12,13} They had demonstrated this benefit if used early and for prolonged periods in patients with severe ARDS. The significant evidence in favor of prone positioning came from Prone Severe ARDS Patients (PROSEVA) trial. Further, a meta-analyses that included PROSEVA⁶ showed that this benefit was seen only if patients had also received low tidal volume during ventilation.^{12,27}

As mentioned earlier, the best support for prone ventilation has come from single large randomized trial, PROSEVA study.⁶ They defined severe ARDS as those who have PaO₂:FiO₂ ratio <150 mmHg on a FiO₂ ≥0.6 and positive

end-expiratory pressure (PEEP) ≥ 5 cm H₂O which is a deviation from the current Berlin definition where severe ARDS is defined as a PaO₂:FiO₂ ratio <100 mmHg. This RCT included 466 patients receiving low tidal volume ventilation for severe ARDS. All patients were kept in supine position for a period of 12–24 hours, a stabilization period before the initiation of prone ventilation. Subsequently, they compared patients receiving prone ventilation with patients ventilated in the supine position. This study showed benefit in the subpopulation of severe ARDS who were ventilated in prone position early (within 33 h of intubation) and for long times (17 consecutive hours) with low tidal volumes. This study showed a reduction in 28-day mortality (16% in prone position vs. 33% in supine position) and 90-day mortality (24% vs. 41%). They did not report any higher risk of complications, and less requirement of rescue therapy in prone position.

There were limitations in PROSEVA trial; 858 of the 1,434 patients with ARDS initially screened were excluded. The exclusion criteria were many, including the use of noninvasive ventilation, inhaled nitric oxide or ECMO before inclusion, raised intracranial pressure, spinal or other fracture instability, deep venous thrombosis treated for less than two days, massive hemoptysis, a mean arterial pressure <65 mmHg, anterior chest tube with leaks, and chronic oxygen-dependent respiratory failure. So, the survival benefit likely applies to a very small select group of ARDS patients. Positive end-expiratory pressure was not optimized prior to the intervention. Patients in supine position had higher sequential organ failure assessment scores. All the sites included in the study had great experience of prone ventilation. The advantage may not apply to facilities with less experience. There is no evidence that prone ventilation prevents organ system dysfunction.^{7–10} Earlier studies have shown that it does not shorten the duration of mechanical ventilation.⁷ However, the large randomized PROSEVA trial⁶ suggested improvement in ventilator-free and time to extubation in the prone position group.

CONTRAINDICATIONS

There are certain conditions where prone positioning is not advised (Box 1). Obesity, patient on continuous renal replacement therapy, and low doses of vasopressors are not contraindications for implementing prone ventilation.

WHEN TO INITIATE PRONE POSITIONING?

This is recommended that one should have low threshold for initiating prone positioning, if indicated in patients of severe ARDS. Early initiation of prone ventilation is most effective as has been shown in many trials. This is more effective as there are more chance of opening of collapse lung in exudative stage. In spite of the fact that there is evidence in support of

Box 1: Absolute and relative contraindications for prone ventilation

Absolute contraindications

- Spinal instability or risk of spinal instability
- Unstable pelvic or facial fractures
- Raised intracranial pressure
- Severe shock
- Pregnancy
- Recent tracheal surgery
- Burns, chest tubes, and open wounds on the anterior chest wall

Relative contraindications

- Hemodynamic or cardiac instability and recent cardiopulmonary arrest
- Thoracic and abdominal surgeries
- Difficult airway or difficult intubation
- Massive hemoptysis requiring an immediate surgical or interventional procedure
- Radiology procedure being planned
- Deep venous thrombosis treated for <2 days
- Lack of experience of the staff
- Tracheal surgery or sternotomy during the previous 15 days
- New tracheostomy (<24 h)
- Increased intraocular pressure
- Cardiac pacemaker inserted in the last 2 days
- Intra-aortic balloon pump
- Advanced osteoarthritis or rheumatoid arthritis

prone ventilation, many centers still do not practice prone positioning.

PRONE POSITIONING: HOW TO DO IT?

Prone Preparation (Box 2)

This can be done manually or by commercially available beds. No protocol or standard method has been recommended for proning procedure. Before turning a patient, it is important to prepare to get good result and avoid failures.

Prone Procedure (Box 3)

Prone is a labor-intensive procedure. This requires coordinated efforts between 4 and 5 persons.²⁸ One person ensures the stability of tube, one person protects the vascular access lines, and in addition, two other staff members turn the patient. A physician who can reintubate the patient should be on the bedside.

It is also important that all staff members should know how to quickly put the patient back into the supine position, particularly required if the patient needs cardiopulmonary resuscitation. This is common to see transient hypoxemia which can be minimized by preoxygenating with a FiO₂ of 1 before turning the patient. Commercially available beds are also available which not only initiate but can also maintain

Box 2: Preparation for proning

- First of all, ensure that there is indication of proning
- Rule out contraindications.
- Explain the procedure to family, its benefit, limitations, and complications
- Order a chest roentgenogram that the tip of the endotracheal tube is located up to 4 cm above the main carina
- Inspect and secure firmly endotracheal tube
- Secure firmly all central and large bore peripheral catheters and chest tubes
- Arrange for support of head, neck and shoulder after proning
- Stop nasogastric tube feeding; evacuate the stomach
- Keep endotracheal suctioning equipment as sometimes there could be copious secretions as soon as you turn the patient
- Make a plan for all intravenous tubing, catheters, and bags as you will have to reposition on the opposite side of the bed
- Assure sufficient tubing length

Box 3: Proning procedure

- Collect 4–5 people who will turn and assign their duties
- Place one person on both sides of the bed who will turn the patient and another at the head of the bed to assure the central lines and the endotracheal tube do not become dislodged or kinked
- Increase the FiO_2 to 1
- Put eye pad for protection of eyes
- Make a note of the ventilator settings
- Pull the patient to the edge of the bed furthest
- Place a new draw sheet on the side of the bed that the patient will face when in this lateral decubitus position
- Turn the patient to the lateral decubitus position with the dependent arm tucked slightly under the thorax
- As the turning progresses, the nondependent arm can be raised over the patient's head or the turn can progress using a logrolling procedure
- Continue turning to the prone position
- Reposition the patient in the center of the bed using sheet
- Turn his/her face toward the ventilator
- Assure that the airway are secured
- Suction the airway, if necessary
- Provide support for the face and shoulders appropriately
- Position the arms for patient's comfort
- Auscultate to check the position of tube
- Check the tidal volume and minute ventilation
- Readjust all tubing, connections and function
- Put electrocardiogram leads on the back
- Document a thorough skin assessment regularly

prone positioning.^{28,29} They avoid risk during turning, and may provide continuous rotation. They have been shown to result in improvement in oxygenation and mortality. No study has compared manual proning to commercial bed turning in order to justify their use.

Ventilatory strategies

Ventilator strategies of invasive mechanical ventilation in the prone position remain the same as that in supine. Low tidal

volume strategy and PEEP similar to patients with ARDS in supine position should be used. One may notice increase in plateau pressure after proning which is due to decreased chest wall compliance and mobilization of secretions. Neuromuscular blocking agents should be used for first 48 hours in patients with P/F ratio <100 .

Monitoring

Monitoring of the patient is same as a patient is monitored in supine position. Electrocardiogram leads are placed on the back. One needs to observe for the copious secretions and the need for suctioning, particularly just after positioning.

On the basis of arterial blood gas changes after prone position, ARDS patients have been classified as “responders” or not “responders”; “ PaO_2 responders” are those whose $\text{PaO}_2/\text{FiO}_2$ ratio increases by at least 20% or by ≥ 20 mmHg. Some consider even 10 mmHg sustained improvement in PaO_2 or increase in lung compliance based on a fall in plateau pressure to be a positive response. The response may be visible in first hour or may be visible after 12–18 hours, provided there is no life-threatening hypoxemia present. Some patients may not show any response. If prone ventilation fails as characterized by either no change or worsening of gas exchange, lung mechanics or cardiovascular status, the patient should be put back to the supine position. In that case, alternate rescue strategies should be thought of.

Feeding and sedation

Prone ventilation can increase residual volume and emesis.^{22,30} Head end of the bed should be kept elevated and prokinetic agent should be used. When patient is repositioned in supine, stomach should be emptied. When patient is put in prone position, requirement of sedation increases. All patients in whom prone ventilation is performed require increased sedation and many require neuromuscular blocking agents. It is convenient to perform all procedures in supine position. One can plan procedures when patient is turned into supine position. Some clinicians have performed bronchoscopy in prone position.

Duration

The duration of prone positioning has varied in different studies. Many of the studies have applied repeated session of 6–8 hours per day. On the other hand, some have used prolonged prone ventilation lasting up to 17–20 hours in 24 hours.^{6,7,10,31}

Proning severe ARDS patients' trial⁶ which showed mortality benefit used mean duration of 17 hours per day in the prone position with an average of total of four sessions. Minimizing the frequency of turning decreases the incidence of complications in these sick patients. So, based on current evidence, it is recommended to maintain prone ventilation for longer periods (17–20 h/day), and supine patient for interventions and nursing.

Box 4: Complications

- Facial edema, conjunctival hemorrhage
- Dislodging endotracheal tube or lines
- Dislodging vascular catheters or drainage tubes
- Worsening in arterial oxygen saturation
- Increased need for sedation or paralysis
- Nerve compression (e.g., brachial plexus injury)
- Retinal damage
- Hemodynamic instability
- Transient arrhythmia
- Diaphragm limitation conjunctival hemorrhage
- Compression of nerves and retinal vessels
- Thoracic drain kinking or obstruction
- Obstruction or kinking of endotracheal tube
- Pneumothorax
- Cardiac events
- Inadvertent dislodging of vascular catheter kinking or removal
- Vascular catheter malfunction during continuous veno-venous hemofiltration
- Deep venous thrombosis
- Urinary bladder catheter or nasogastric feeding tube displacement
- Enteral nutrition intolerance
- Difficulty in instituting cardiopulmonary resuscitation

COMPLICATIONS^{32,33} (BOX 4)

The centers with experience in prone positioning can minimize life-threatening complications. There are complications that can occur which are preventable. The most common side effect seen after proning are related to pressure point-related side effects like dependent facial and ocular edema, skin breakdown, and brachial plexus neuropathy. These can be minimized by frequent repositioning and soft padding. It is also important to increase awareness of providers. The pressure ulcers occur on the anterior shoulder, chest, knee, and face. Male gender aged ≥ 60 years and body mass index less than 28.4 are the risk factors for complications. The rate of expected complications (e.g. unplanned extubation, endotracheal tube obstruction, hemoptysis, arterial desaturations, bradycardia, and severe hypotension) was no different between the groups in PROSEVA trial.⁶

CONCLUSION

Prone ventilation, the delivery of mechanical ventilation with the patient lying in the prone position, is now an established procedure which not only results in improved oxygenation but also improves survival in a select population of patients with moderate and severe ARDS. This should always combined with low tidal volume strategy. Initially, all patients should be ventilated in supine position using lung-protective strategy. If this strategy fails and the patient has refractory hypoxemia, he should be given a trial of prone positioning. It is advisable to implement prone ventilation early in the course of ARDS

(within the first 36 h). The best results are achieved if patient is prone for 18–20 consecutive hours. However, it is not certain that benefit apparent in the PROSEVA trial can be replicated in centers with less expertise and further research is warranted.

REFERENCES

1. Koulouras V, Papathanakos G, Papathanasiou A, et al. Efficacy of prone position in acute respiratory distress syndrome patients: A pathophysiology-based review. *World J Crit Care Med*. 2016;5:121-36.
2. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med*. 1998;157:387-93.
3. Mure M, Martling CR, Lindahl SG. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. *Crit Care Med*. 1997;25:1539-44.
4. Blanch L, Mancebo J, Perez M, et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med*. 1997;23:1033-9.
5. Jolliet P, Bulpa P, Chevreton JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med*. 1998;26:1977-85.
6. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159-68.
7. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2009;302:1977-84.
8. Guérin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA*. 2004;292:2379-87.
9. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med*. 2001;345:568-73.
10. Mancebo J, Fernández R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2006;173:1233-9.
11. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med*. 2008;36:603-9.
12. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med*. 2014;40:332-41.
13. Lee JM, Bae W, Lee YJ, Cho YJ. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med*. 2014;42:1252-62.
14. Mora-Arteaga JA, Bernal-Ramírez OJ, Rodríguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. *Med Intensiva*. 2015;39:359-72.
15. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology*. 1974;41:242-55.
16. Pelosi P, Croci M, Calappi E, et al. Prone positioning improves pulmonary function in obese patients during general anesthesia. *Anesth Analg*. 1996;83:578-83.
17. Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med*. 2000;161:1660-5.
18. Nyrén S, Radelli P, Lindahl SG, et al. Lung ventilation and perfusion in prone and supine postures with reference to anesthetized and mechanically ventilated healthy volunteers. *Anesthesiology*. 2010;112:682-7.
19. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J*. 2002;20:1017-28.
20. Cornejo RA, Díaz JC, Tobar EA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2013;188:440-8.
21. Chatte G, Sab JM, Dubois JM, et al. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med*. 1997;155:473-8.

22. Fridrich P, Krafft P, Hochleuthner H, et al. The effects of long-term prone positioning in patients with trauma-induced adult respiratory distress syndrome. *Anesth Analg.* 1996;83:1206-11.
23. Gattinoni L, Mascheroni D, Torresin A, et al. Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. *Intensive Care Med.* 1986;12:137-42.
24. Lim CM, Kim EK, Lee JS, et al. Comparison of the response to the prone position between pulmonary and extrapulmonary acute respiratory distress syndrome. *Intensive Care Med.* 2001;27:477-35.
25. Mure M, Glenn RW, Domino KB, et al. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med.* 1998;157:1785-90.
26. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med.* 1998;157:387-93.
27. Park SY, Kim HJ, Yoo KH, et al. The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *J Thorac Dis.* 2015;7:356-67.
28. Messerole E, Peine P, Wittkopp S, et al. The pragmatics of prone positioning. *Am J Respir Crit Care Med.* 2002;165:1359-63.
29. Vollman KM, Bander JJ. Improved oxygenation utilizing a prone positioner in patients with acute respiratory distress syndrome. *Intensive Care Med.* 1996;22:1105-11.
30. Reigner J, Thenoz-Jost N, Fiancette M, et al. Early enteral nutrition in mechanically ventilated patients in the prone position. *Crit Care Med.* 2004;32:94-9.
31. Saez de la Fuente I, Saez de la Fuente J, et al. Enteral Nutrition in Patients Receiving Mechanical Ventilation in a Prone Position. *JPEN J Parenter Enteral Nutr.* 2016;40:250-5.
32. Girard R, Baboi L, Ayzac L, et al; Proseva trial group. The impact of patient positioning on pressure ulcers in patients with severe ARDS: results from a multicentre randomised controlled trial on prone positioning. *Intensive Care Med.* 2014;40:397-403.
33. Panchabhai TS, Bandyopadhyay D, Kapoor A, et al. Acute ischemic optic neuropathy with extended prone position ventilation in a lung transplant recipient. *Int J Crit Illn Inj Sci.* 2016;6:45-7.

Viral Pneumonia

Ruchira W Khasne

INTRODUCTION

Although severe community acquired pneumonia (CAP) is caused by bacteria, in recent years, viruses have been identified as frequent cause of CAP. In adults, the most common cause of viral pneumonia in community is influenza virus type A and B.¹ Depending on the virulence of the organism as well as the age and comorbidities of the patient, viral pneumonia can vary from a mild and self-limited illness to a life-threatening disease. In immunocompromised patients, viral pneumonia may result in respiratory failure, severe hypoxemia, and acute respiratory distress syndrome (ARDS).

EPIDEMIOLOGY² (TABLE 1)

Viruses with known etiology account for 15–40% of all cases of serious CAP requiring hospitalization, of which influenza A and B being the most common³ in developing countries, incidence is five times higher than in developed regions.¹ Most of the infective viruses are constantly present in human or animal reservoirs. Under some circumstances, they are transmitted to susceptible host. The highest incidences arise in children younger than 5 years and in adults older than 75 years.¹ Few viruses have potential to cause epidemic like influenza A and B, measles, severe acute respiratory syndrome (SARS) due to aerosol transmission. In the

TABLE 1 Epidemiology of viral pneumonia

Virus	Family	Periodic changes	Epidemics
Novel influenza A (H1N1) virus caused a worldwide pandemic	RNA A, B, and C subtypes Orthomyxoviridae family	Annual winter epidemics occur predictably, lasting 6–8 weeks, time of onset, and severity are highly variable. Outbreaks occur in closed settings	Maintains infectivity by antigenic drift (epidemics), alteration in proteins structure (pandemics 2009)
Rhinovirus	RNA Picornaviridae	Affects all ages, circulate throughout the year, but activity peaks in the fall and spring. Most children are infected before age 5 years, reinfection in older children and young adults	Outbreaks in long-term care facilities, day-care centers
Respiratory syncytial virus	RNA Paramyxoviridae family	Respiratory syncytial virus has become an increasingly important pathogen in the elderly population, COPD, post lung transplant	Does not undergo major periodic antigenic changes, immunity is incomplete
Parainfluenza virus	RNA Paramyzoviridae family	Seasonal outbreak occurs in fall and spring, outbreak of invasive pneumococcal disease in a long-term care facility	–
Adenovirus	DNA virus Adenoviridae	Can occur at any time of the year. Disease at military recruit training facilities in the United States and worldwide	–
Measles	RNA Paramyzoviridae family	Pregnant patients, highly contagious	–
Varicella zoster virus	DNA Herpesviridae	Pregnancy, hematologic malignancies, and patients with organ transplant lead to life-threatening complications	–

Continued

Continued

Virus	Family	Periodic changes	Epidemics
Coronavirus	RNA Coronaviridae	Late winter and early spring, demonstrating 2–3 years periodicity. Severe acute respiratory syndrome	Epidemic of 2003 in southern China and Asia (severe acute respiratory syndrome)
Cytomegalovirus	DNA Herpesviridae	Hematopoietic stem cell transplant, heart lung transplant recipients (highest peak in 1–3 months post-transplant) and in human immunodeficiency virus	–
Herpes simplex virus	DNA Herpesviridae	In transplant patients but rare	–
Human metapneumovirus	RNA Paramyxo	Temperate climates in winter months	Recently identified

RNA, ribonucleic acid; DNA, deoxyribonucleic acid

TABLE 2 Mode of transmission of virus

Immune status	Organism	Mode of transmission
Immunocompetent	Influenza (H1N1), Adenovirus	<ul style="list-style-type: none"> • Small particle aerosol spread • Healthcare personnel (Adenovirus)
	Avian Influenza (H5N1)	<ul style="list-style-type: none"> • Environmental contamination • Live bird-reservoir
	Respiratory syncytial virus, Rhinovirus	<ul style="list-style-type: none"> • Large droplet • Fomites • Hand contact (Healthcare personnel-respiratory syncytial virus)
	Parainfluenza virus	<ul style="list-style-type: none"> • Healthcare personnel
	Measles	<ul style="list-style-type: none"> • Healthcare personnel
	Cytomegalovirus	<ul style="list-style-type: none"> • Transplantation of contaminated organs/blood products • Lower respiratory aspiration of virus asymptotically present in saliva • Reactivation of latent infection • Hematogenous spread
Immunocompromised	Herpes simplex virus	<ul style="list-style-type: none"> • Lower respiratory aspiration of virus asymptotically present in saliva • Reactivation of latent infection
	Varicella zoster virus	<ul style="list-style-type: none"> • Direct contact with contaminated objects
	Coronavirus	<ul style="list-style-type: none"> • Healthcare personnel, droplet
Emerging	Hantavirus	<ul style="list-style-type: none"> • Inhalation of infected excreta of diseased rodents

absence of antiviral treatment, viral shedding starts within 24 hours before the onset of symptoms and continues for approximately 5 days in healthy adults.⁴ Use of antiviral medications, within the first 48–96 hours of illness, reduces this infectious period.⁵ Modes of transmission are described in table 2.

PATHOGENESIS

- The viral infection initiated in and primarily confined to the respiratory tract, so-called primary viral pneumonia, e.g., influenza or respiratory syncytial virus (RSV)
- Pneumonia as a significant life-threatening complication of infection with subsequent systemic manifestation in

otherwise healthy adults and immunocompromised hosts (including pregnant women), e.g., measles or Varicella zoster virus (VZV)

- Respiratory tract involvement secondary to a systemic infection. *Cytomegalovirus* (CMV) pneumonitis is a complex interaction between viral infection and graft versus host disease, particularly in bone marrow transplant patients.

Each of these situations may lead to what is recognized clinically as a viral pneumonia.⁶ Viral infections cause degeneration and cellular necrosis of infected cells, leading to local and systemic inflammatory response. Respiratory epithelial cells are invaded and viral replication occurs. Alveolar spaces are flooded with varying number of

neutrophils and mononuclear cells admixed with fibrin and edema fluid. The alveolar capillaries are hyperemic and associated with intra-alveolar hemorrhage. The body's defense mechanisms include phagocytosis, humoral and cell mediated responses, and production of interferons.

CLINICAL MANIFESTATIONS

In viral infections, respiratory tract shows wide spectrum of clinical entities including croup and bronchiolitis, tracheobronchitis, and reactive airways, and pneumonitis depends on presence or absence of risk factors (Box 1). The common constitutional symptoms are fever, chills, nonproductive cough, rhinitis, myalgias, headache, and fatigue. On examination, patient can have tachypnea and/or dyspnea, desaturation, tachycardia or bradycardia, wheezing, rhonchi, rales, cyanosis, and rash.

DIFFERENT VIRAL ETIOLOGY AND CLINICAL FEATURES

Viral Pneumonia in Immunocompetent Individuals

Most of the viral pneumonia in this group is caused by influenza A and B, H5NI, RSV, parainfluenza virus (PIV), adenovirus, measles, VZV, and emerging viruses like *Hantavirus* and Human SARS *Coronavirus*.⁶

Influenza Virus

It is the seasonal "flu" virus and the most common viral cause of pneumonia. It has two envelope glycoproteins, hemagglutinin and neuraminidase. Two influenza types have emerged of particular importance: (i) H1N1 (swine influenza strain) and (ii) H5N1 (avian influenza strain). The H1N1 virus rapidly spread to become a worldwide pandemic in 2009. The World Health Organization (WHO) declared an end to the pandemic in August 2010. Patient may appear acutely ill with constitutional symptoms, which last for 3–5 days. The systemic symptoms like feverishness, headache, chills,

myalgia, malaise, and nonproductive cough, which usually persist for 3–4 days. Small proportion of infection can lead to complications such as respiratory failure, ARDS, sepsis, and secondary bacterial pneumonia, which is characterized by the relapse of high fever, cough with purulent sputum after initial improvement, and radiographic evidence of new pulmonary infiltrates. The most common pathogen is *Streptococcus pneumoniae*, followed by *Staphylococcus aureus*,⁷ *Haemophilus influenzae*, and Gram-negative pathogens.

H5N1 Virus

It was previously known to infect only birds but now found to infect humans. Its incubation period is 2–5 days. Manifestations are the same as that of seasonal influenza and may lead to fatal ARDS or multisystem organ failure and disseminated intravascular coagulation.⁸

Respiratory Syncytial Virus

It is the most frequent cause of lower respiratory tract infection among infants and children. In adults, it is the second most common viral cause of pneumonia. It causes syncytia formation in cell culture, giving the virus its name.

Parainfluenza Virus

It is the most common cause of croup and bronchiolitis in children. In adults, its manifestation may vary from milder form to a life-threatening pneumonia with lung injury, especially in immunocompromised hosts.

Adenovirus

In children, it is known to cause pharyngoconjunctival fever. In fatal cases, it manifests with extensive pulmonary damage and coagulopathy. Other nonrespiratory symptoms like diarrheal illness, hemorrhagic cystitis, and epidemic keratoconjunctivitis are seen in adults.

Measles

It is manifested as severe pneumonitis with rash in children. It causes severe lower respiratory tract infection in immunocompromised host with bacterial superinfection.

Varicella zoster Virus

It primarily manifests as chicken pox, which is characterized by a rash. Pneumonia is apparent 1–6 days after the onset of rash. There is no correlation of pneumonia with severity of rash. Reactivation is seen in immunocompromised patients.

Box 1: Risk factors for viral pneumonia

- Advance age
- Smoking
- Chronic disorders like heart disease
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Renal disease
- Immunosuppression-like blood disorder and malignancy
- Obesity
- Pregnancy

Emerging Viruses Causing Pneumonia

Viruses, which are endemic but having epidemic potential,⁹ are described next.

Hantavirus Pulmonary Syndrome

It produces hemorrhagic fever with renal failure syndrome and *Hantavirus* cardiopulmonary syndrome. Blood investigation shows triad of thrombocytopenia, left shift with circulating myeloblast, and circulating immunoblasts. The case fatality averages approximately 30–40%.⁶

Human Coronavirus

It exhibits biphasic course with prodromic manifestations, which progresses to ARDS. Its transmission is halted largely due to aggressive infection control practices. Laboratory investigations show increased lactate dehydrogenase, transaminase, creatine kinase, thrombocytopenia, and lymphopenia with depletion of CD4 and CD8 cells.^{6,10}

Viral Pneumonia in Immunocompromised Individuals

Host with diminished immunity may develop severe life-threatening pulmonary infections. Deoxyribonucleic acid viruses have received more recognition in this regard.

Cytomegalovirus

Primary CMV infection remains latent. It gets reactivated in immunosuppressed host. The severity of pneumonia is related to the intensity of immunosuppression. Reactivation occurs between 14 and 21 days of intensive care unit stay. Involvement of lung parenchyma with marked hypoxemia is an indicator of life-threatening infection. It is accompanied by neutropenia, thrombocytopenia, and elevated liver enzymes.

Herpes Simplex Virus

Herpes simplex virus is a rare cause of lower respiratory tract infections and is seen primarily in severely immunocompromised patients. Pneumonia may develop from primary infection or reactivation.

Human Metapneumovirus

Newly discovered ubiquitous is reported to cause infection in children like bronchiolitis, croup, asthma, and pneumonia. The severity of infection increases with older age and with comorbidity, or immunosuppressive conditions lead to severe pneumonitis.¹¹

RADIOLOGICAL DIAGNOSIS (FIGS 1 AND 2)

Radiographic findings are not virus specific. They are variable and overlapping with bacterial pneumonia, but in combination with clinical findings, they can substantially improve the accuracy of diagnosis.¹² In healthy individual, it can present like an “atypical” pneumonia while in immunocompromised host can present as a severe lobar or bilateral pneumonia.

Chest Radiographs

Normal findings or unilateral or patchy bilateral areas of consolidation, nodular opacities, bronchial wall thickening,



FIG. 1: Frontal radiograph of a 21-year old male with fever and cough for 3 days, showing increased parahilar and basilar interstitial markings with few vague hazy nodules, suggestive of infective etiology



FIG. 2: Axial nonenhanced computed tomography section showing peribronchial, patchy, ground-glass opacities, in lobular distribution in a 19-year old female with H1N1 infection

and small pleural effusions. Lobar consolidation is uncommon in patients with viral pneumonia but in a few cases, rapid progression to ARDS is noted.

Computed Tomography¹²

- Parenchymal attenuation disturbances: Involved lung parenchyma appears as areas of patchy inhomogeneities (mosaic attenuation pattern) whereas an uninvolved segment shows normal or increased attenuation
- Ground-glass opacity and consolidation: Coexisting thickening of the interstitium and partial filling of the airspaces may contribute to ground-glass opacity (hazy increase in attenuation) and consolidation
- Nodules and micronodules: Nodules smaller than 10 mm in diameter are suggestive of viral etiology, appear as dense and of homogenous attenuation or show ground-glass opacity
- Interlobular septal thickening: Presence of interstitial fluid, cellular infiltration is seen as interstitial thickening.
- Bronchial and/or bronchiolar wall thickening: Inflammation and fibrosis lead to bronchial wall thickening.

LABORATORY DIAGNOSIS (TABLE 3)

An accurate and early etiologic diagnosis is important because specific therapies are used against certain viruses. Polymerase chain reaction and reverse-transcriptase (RT-PCR) are the most sensitive and specific methods. Nasopharyngeal and nasal specimens are generally preferred than throat swab specimens,¹³ but endotracheal or bronchoscopic aspirates have higher yields.¹⁴ As per Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) guidelines, the tests depicted in table 3 may be performed for diagnosis of viral pneumonia.^{15,16} Advantage of quantitative PCR is additional measurement of viral

load. Intranuclear or cytoplasmic inclusions in respiratory specimen are diagnostic.¹⁷

ANTIVIRAL THERAPY

Influenza

The currently circulating 2009 H1N1 virus is susceptible to neuraminidase inhibitor (NAI) (oseltamivir and zanamivir) which are active against both influenza A and B viruses and matrix-2 (M2) inhibitors (amantadine and rimantadine) which are active against all influenza A strains, but have no activity against influenza B viruses.¹⁸⁻²⁰ WHO has recommended guidelines for prevention and treatment for influenza pneumonia.²¹ Antiviral therapy with NAI within 48 hours of the onset of influenza illness is recommended to reduce the duration of symptoms, severity, and risk of complications without waiting for laboratory results.²² Early therapy reduces duration of viral shedding, days of hospitalization, progression to severe disease, or resulting death.^{23,24} Adults with increased risk for complicated illness, NAI should be started without delay for pending laboratory diagnosis.

Usual dosing of oseltamivir for treatment of influenza is 75 mg orally twice a day and zanamivir is 10 mg (2 inhalations) twice a day for 5 days although longer treatment may be considered. In healthy patient with uncomplicated illness, NAI should be considered depending upon clinical judgment. Patient with severe progressive disease requiring hospitalization doubling the dose to 150 mg twice a day for 10 days in severe cases of H1N1²¹ and H5N1^{25,26} have been administered successfully. Controlled studies of doses up to 450 mg twice daily have been administered in healthy adults successfully.²⁷ In pregnant patients, oseltamivir for 10 days or zanamivir should be considered as early as possible at onset of illness.

TABLE 3 Laboratory diagnosis of viral pneumonia

Method	Immunological technique			Molecular	Microbiological
	Rapid influenza diagnostic test	Immuno-fluorescence	Serologic tests	Reverse transcriptase-polymerase chain reaction	Viral culture (Gold Standard)
Test time	15 min	1-4 h	2 weeks	1-6 h	1-10 days
Specimen	Respiratory samples	Respiratory samples	Serum	Respiratory samples	Respiratory samples
Sensitivity	+ (0-20%)	++	n/a	+++ (10-80%)	++
Specificity	+++ (>90%)	+++	n/a	++++ (95-100%)	++++
Distinguishes influenza A from B	Yes	Yes	Yes	Yes	
Influenza A subtypes	No	No	Yes	Yes	
Limitations	Subtype cannot be obtained Overall sensitivity is lower than viral cultures	Cannot identify subtypes	Longer duration for test results Requires pair and convalescent sera and fourfold rise	Expensive Not useful in patients who shed infection for long periods	Takes long time Needs specific culture medium

Resistance

Most of the circulating strains of the novel H1N1 influenza A virus are sensitive to the NAI, but that nearly all strains were resistant to the amantadine.²⁸ Advisory Committee on Immunization Practices recommends not to use M2 inhibitors for treating influenza. Viral neuraminidase mutations lead to resistance to oseltamivir, but not to inhaled zanamivir in uncomplicated illness.²⁰ Resistance is seen in those who are immunocompromised and received oseltamivir for prolonged period.

Novel Antiviral Treatment

- **Peramivir (NAI):** Intravenous peramivir (600 mg) single dose was authorized for hospitalized patients in 2009 H1N1 pandemic influenza²⁹
- **Laninamivir (NAI):** Laninamivir octanoate in inhaled form is for the treatment of seasonal influenza in adults and its effectiveness is also shown for the oseltamivir resistant virus³⁰
- **Favipiravir (T-705):** It has been shown to inhibit a variety of influenza viruses, including highly pathogenic avian influenza H5N1 viruses.

Antivirals such as entry inhibitors, nucleoside analogs like cidofovir, viral enzyme inhibitors (such as terminase and helicase enzyme inhibitors), and translation inhibitors may be utilized in an offlabel indication for treatment of viral infections.²⁹ Efficacy of oseltamivir-zanamivir combinations for seasonal influenza is not yet established.³¹ Zanamivir dry powder should not be administered by nebulization as the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.³²

- **Avian influenza (H5N1):** WHO recommends consideration of higher dosage of oseltamivir (150 mg per os twice daily) and longer duration in severe infections. Thus, for resistant strains, consideration for combination therapy with NAI-adamantane or oseltamivir-ribavirin, or even triple therapy with NAI-adamantane-ribavirin, should be given⁸
- **Respiratory syncytial virus:** Current recommendations are that high dose aerosolized ribavirin therapy should be considered only for severe RSV infection and in high risk patients with high mortality, such as hematopoietic stem cell transplantation (HSCT) recipients.³³ However, there is little evidence for the efficacy.⁶ Respiratory syncytial virus-specific intravenous immunoglobulin, such as palivizumab is used with aerosolized and oral ribavirin in high risk patients, such as HSCT recipients, appears to be promising
- **Parainfluenza virus:** Treatment is mainly supportive. The use of ribavirin may be reasonable³⁴
- **Adenovirus:** Antiviral treatment of proven value is not available. Routine use of ribavirin is not recommended.

Cidofovir and ganciclovir may be useful in seriously ill patients⁶

- **Measles:** Aerosolized or intravenous ribavirin may reduce the severity of symptoms in children and some immunocompromised patients with pneumonia have done well
- **Varicella zoster virus:** Varicella pneumonia in patients who are immunocompromised, acyclovir (10 mg/kg intravenous every 8 hours for 7 days) has been shown to be effective
- **Hantavirus disease:** Intravenous ribavirin is effective in the treatment
- **Coronavirus:** Proven antivirals are currently unavailable. The most promising to date appears to be the type-I interferons (α and β), which are highly active in cell culture
- **Cytomegalovirus:** Ganciclovir as a preemptive therapy and as prophylaxis is effective for prevention of symptomatic CMV infections in nonimmunocompromised patients. In lung transplant recipients, ganciclovir with CMV immunoglobulin has been associated with increased survival by ameliorating graft versus host disease.³⁵ Cidofovir, foscarnet, and fomivirsen are approved for CMV, but their effectiveness for treating CMV pneumonia has not been established⁶
- **Herpes simplex virus:** Intravenous acyclovir has been effective when initiated early in the course of varicella pneumonia. Famciclovir and penciclovir are similar to acyclovir in their spectrum of activity against herpes viruses
- **Human metapneumovirus:** Ribavirin has activity against human metapneumovirus.

GENERAL TREATMENT CONSIDERATIONS

Respiratory Support for Critically Ill Patients

Rapidly progressive respiratory failure with increased requirement of fraction of inspired oxygen to maintain oxygen saturation with ARDS should be admitted in critical care unit. Those patients who require invasive mechanical ventilatory support should be managed with low tidal volume (6 mL/kg predicted body weight) lung protective ventilator strategy with plateau pressure <30 cmH₂O as per Acute Respiratory Distress Network (ARDSNet) study.³⁶ Restricted fluid strategy to improve oxygenation and more ventilator free days.³⁷ In case of refractory hypoxemia prone ventilation,³⁸ extracorporeal membrane oxygenation are recommended.³⁹ Noninvasive ventilation is not recommended in viral pneumonia, which is complicated by ARDS.

Antibiotics

Bacterial coinfection may occur with severe viral pneumonia. Based on local epidemiological and microbiological data,

empiric treatment for CAP as per published guidelines should be started till pending diagnostic tests.⁴⁰ Antibiotics should not be used as a chemoprophylaxis for viral pneumonia.

Steroids

Moderate-to-high doses of systemic steroids are not recommended in viral pneumonia. They are of unproven benefit and potentially harmful.⁴¹ Low dose steroids should be considered in severe influenza with septic shock, but it requires further investigations. It is associated with delayed clearance of viruses⁴² and invasive fungal infections.⁴³

Antipyretics

Give paracetamol (acetaminophen) as an antipyretic orally or by suppository. Avoid administration of salicylates in children and young adults (<18 years old) due to the risk of Reye's syndrome.

Other Immunomodulating Therapies

Case control studies suggested that use of plasma and immunoglobulin (intravenous immunoglobulin) have favorable response in H1N1 and H5N1 patients but needs further evaluation.⁴⁴ Role of passive immunomodulating agents, like statins, gemfibrozil, and N-acetyl-L-cysteine requires further investigations.^{32,45,14}

COMPLICATIONS AND TREATMENT OF COMPLICATIONS⁴⁶

Pulmonary Complications

Secondary Bacterial Pneumonia

The most common bacteria responsible for bacterial pneumonia complicating influenza are *Streptococcus pneumoniae*, *Staphylococci*, and *Haemophilus influenzae* in a relative frequency. Chest X-ray reveals lobar infiltrates and the clinical course is typical of bacterial pneumonia. Usually, patients respond well to antibiotics.

Mixed Viral and Bacterial Pneumonia

Patient shows clinical features of both primary and secondary pneumonia. Causative organisms and treatment is similar like bacterial superinfection.

Nonpulmonary Complications

Myositis

Myositis and myoglobinuria with tender leg muscles and elevated serum creatine phosphokinase levels have been reported, mostly in children but in adults as well.⁴⁷

Cardiac Complications

Both myocarditis and pericarditis have been rarely associated with influenza A or B virus infection.

Toxic Shock Syndrome

This is characterised by generalised maculopapular rash which exfoliates along with features of septic shock.

Central Nervous System Complications

Guillain-Barré syndrome has been reported to occur after influenza A infection. Cases of transverse myelitis and encephalitis have occurred, rarely reported.

Reye's Syndrome

Reye's syndrome is associated with influenza B and varicella in children who received aspirin for febrile illness. The classic manifestations range from lethargy to delirium, obtundation, seizures, and respiratory arrest. Lumbar puncture reveals normal protein values and normal cell count. The most frequent laboratory abnormality is elevation of the blood ammonia value, which occurs in almost all patients. Influenza vaccination reduces the risks of Reye's syndrome.

Chemoprophylaxis

As per CDC, chemoprophylaxis should be started within 48 hours of exposure. All four antiviral agents are effective:

- Seasonal prophylaxis: Drug to be administered throughout epidemic exposure, generally 4-6 weeks
- Family prophylaxis: Drug to be administered to all family members for a short period after recognition of index case in that family
- Outbreak prophylaxis: During outbreaks, everyone in the institution should receive prophylactic therapy for 2 weeks for termination of transmission
- Postexposure prophylaxis: Antivirals have been started within 48 hours of recent exposure and should be continued for minimum of 2 weeks.

PREVENTION AND VACCINATION⁴⁸ (TABLE 4)

The most important preventive measure for influenza infections is annual immunization as per CDC and IDSA guideline.^{16,25} Prevention of transmission requires early recognition of symptoms, prompt institution of appropriate transmission based precautions, and adherence to basic infection control practices such as hand hygiene. As per WHO guidance, use a particulate respirator like N95 with eye protection, gowns, and gloves while performing high risk aerosol generating procedures like bronchoscopy or any procedure involving aspiration of the respiratory tract.

TABLE 4 Influenza vaccination

	Inactivated influenza vaccine	Live attenuated influenza vaccine
Type	Killed virus	Live attenuated
Route of administration	Intramuscular (anterolateral aspect of the thigh)	Intranasal spray
Frequency	Once a year	Once a year
Age group	>6 months and high risk conditions	Healthy persons between 5 years and 49 years age, Nonpregnant and health care workers
Signs and symptoms	No signs and symptoms	May produce, mild signs and symptoms
Contraindications	History of severe allergic reaction to any component of the vaccine	For the 2016–17 season, Advisory Committee on Immunization Practices recommends that live attenuated influenza vaccine not be used

These isolation precautions should be continued for either 7 days after the onset of illness or 24 hours after resolution of fever and respiratory symptoms, whichever is longer. Respiratory isolation is not required for the respiratory viruses, which spread via fomites and large particle droplets.⁵ Immunosuppressed patients shed virus for a longer time period. They are also at increased risk for development of antiviral-resistant virus hence needs more attention.⁴¹

CONCLUSION

Viruses are the smallest infective agents which are omnipresent. They have survived the evolution because of their ability to undergo mutations and alterations in their genetic structure.

Viruses, as a cause of community acquired or nosocomial infection may be just a tip of the iceberg. Better availability of molecular diagnostics enables us to reassess all existing dogma in management of viral sepsis. Newer modalities should guide us in quicker diagnosis and appropriate antiviral drugs. Thus it can avoid unnecessary use of antibiotics and emergence of multidrug-resistance organisms.

REFERENCES

- Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet*. 2011; 377(9773):1264-75.
- Falsey AR, Walsh EE. Viral Pneumonia in older adults. *Clin Infect Dis*. 2006;42(4):518-24.
- Johnstone J, Majumdar SR, Fox JD, et al. Viral Infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest*. 2008;134(6):1141-8.
- Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: A review of volunteer challenge studies. *Am J Epidemiol*. 2008;167(7):775-85.
- Lee N, Chan PKS, Hui DSC, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. 2009;200(4):492-500.
- Grippi M, Elias J, Fishman J, et al. *Fishman's Pulmonary Diseases and Disorders*. (volume 1), 5th edition. New York: McGraw Hill Professional; 2015. pp. 2388-95.
- Kallen AJ, Brunkard J, Moore Z, et al. *Staphylococcus aureus* community-acquired pneumonia during the 2006 to 2007 influenza season. *Ann Emerg Med*. 2009;53(3):358-65.
- Uyeki TM. Human infection with highly pathogenic avian influenza A (H5N1) virus: review of clinical issues. *Clin Infect Dis*. 2009;49(2):279-90.
- Al Rabeeah AA, Cummings DA, Alabdullatif ZN, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med*. 2013;369(5):407-16.
- Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348(20):1986-94.
- Falsey AR, Erdman D, Anderson LJ, et al. Human metapneumovirus infections in young and elderly adults. *J Infect Dis*. 2003;187(5):785-91.
- Franquet T. Imaging of pulmonary viral pneumonia. *Radiology*. 2011;260(1):18-39.
- Heikkinen T, Salmi AA, Ruuskanen O. Comparative study of nasopharyngeal aspirate and nasal swab specimens for detection of influenza. *BMJ*. 2001;322(7279):138.
- WHO Geneva. (2007). Clinical management of human infection with avian influenza A (H5N1) virus. [online] Available from: <http://scholar.google.com/>. [Accessed September, 2016].
- Marzoratti L, Iannella HA, Fernández Gómez V, et al. Recent Advances in the diagnosis and treatment of influenza pneumonia. *Curr Infect Dis Rep*. 2012;14(3):275-83.
- Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(8):1003-32.
- Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RTR, Werno AM, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax*. 2008;63(1):42-8.
- Fiore AE, Fry A, Shay D, Gubareva L, et al. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1-24.
- Centers for Disease Control and Prevention (CDC). National and state vaccination coverage among adolescents aged 13 through 17 years—United States, 2010. *Morb Mortal Wkly Rep*. 2011;60(33):1117-52.
- Teo KK, Pogue J, Dyal L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *Hosp Med*. 2008;2008:1547-59.
- World Health Organization. (2010). Guidelines for Pharmacological Management of Pandemic Influenza A (H1N1) 2009 and other Influenza Viruses. [online] Available from http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/. [Accessed September, 2016].
- Maruyama T, Fujisawa T, Suga S, et al. Outcomes and prognostic features of patients with influenza requiring hospitalization and receiving early antiviral therapy a prospective multicenter cohort study. *Chest*. 2016;149(2):526-34.
- Cooper NJ, Sutton AJ, Abrams KR, et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2003;326(7401):1235.
- Louie J, Jamieson DJ, Honein MA. Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. *N Engl J Med*. 2010;362(1):27-35.
- Frieden TR, Harold Jaffe DW, Stephens JW, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention *MMWR*. 2011;60(1):1-18.
- Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. *Int J Antimicrob Agents*. 2010;35(5):461-7.
- Bautista E, Chotpitayasunondh T, Gao Z, et al. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) virus infection. *N Engl J Med*. 2010;362(18):1708-19.

28. Hayden FG, De Jong MD. Emerging influenza antiviral resistance threats. *J Infect Dis*. 2011;203(1):6-10.
29. De Clercq E. Antivirals: past, present and future. *Biochem Pharmacol*. 2013;85(6):727-44.
30. Watanabe A, Chang S, Kim MJ, et al. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: A double-blind, randomized, noninferiority clinical trial. *Clin Infect Dis*. 2010;51(10):1167-75.
31. Duval X, van der Werf S, Blanchon T, et al. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal influenza: A randomized placebo-controlled trial. *PLoS Med*. 2010;7(11):e1000362.
32. Hui DS, Lee N, Chan PKS. Clinical management of pandemic 2009 influenza A(H1N1) infection. *Chest*. 2010;137(4):916-25.
33. Dowell SF, Anderson LJ, Gary HE, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. *J Infect Dis*. 1996;174(3):456-62.
34. Chakrabarti S, Collingham KE, Holder K, et al. Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation: a pilot study. *Bone Marrow Transplant*. 2001;28(8):759-63.
35. Zamora MR. Cytomegalovirus and lung transplantation. *Am J Transplant*. 2004;4(8):1219-26.
36. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-8.
37. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-75.
38. Girard R, Gacouin A, Guérin C, et al. Prone Positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-68.
39. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-63.
40. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. 2007;44(Suppl 2):S27-72.
41. World Health Organization. (2009). Clinical management of human infection with pandemic (H1N1) 2009: revised. [online] Available from: http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf. [Accessed September, 2016].
42. Buckingham SC, Jafri HS, Bush AJ, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. *J Infect Dis*. 2002;185(9):1222-8.
43. Lat A, Bhadelia N, Milko B, et al. Invasive aspergillosis after pandemic (H1N1) 2009. *Emerg Infect Dis*. 2010;16(6):971-3.
44. Hung IFN, To KKW, Lee C-K, et al. Hyperimmune IV immunoglobulin treatment. *Chest*. 2013;144(2):464-73.
45. Boyd AR, Mortensen EM. Are statins beneficial for viral pneumonia? *Eur Respir J*. 2013;41(5):1010-1.
46. Mandell GL, Dolin R, Bennett JE. Principles and practice of infectious diseases Vol. 1, 7th edition. Philadelphia: Elsevier; 2010. pp. 1689-99.
47. Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. *Clin Microbiol Rev*. 2008;21(3):473-94.
48. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines. *MMWR Recomm Reports*. 2016;65(5):1-54.

Corticosteroids in Severe Community-acquired Pneumonia: Current Status

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INTRODUCTION

Pneumonia is one of the most common infectious diseases seen in hospital practice. Prognosis of pneumonia varies considerably from a mild self-limiting disease to a severe life-threatening condition. Up to 10% of patients with community-acquired pneumonia (CAP) require intensive care unit (ICU) admission with an overall 28-day mortality of 12–36%;^{1,2} mortality increases to 25% in patients requiring invasive mechanical ventilation and 28.8% if septic shock is present.² As in other severe bacterial infections, an excessive systemic inflammatory response is believed to contribute to mortality in pneumonia.³ Corticosteroids can modulate inflammation, suppress the immune system and regulate stress response.⁴ Two recent studies suggest that corticosteroids may have a role in the treatment of CAP.^{1,5} We review here the current evidence and recommendations for the role of steroids in CAP.

CORTICOSTEROIDS IN INFECTION AND SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The innate immune response plays an important role in acute bacterial infections.^{4,6,7} Cytokines play an essential role in clearing pathogens, repairing lung tissue, and modulating inflammatory response.⁸ During early infection, alveolar macrophages produce proinflammatory cytokines and chemokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1, IL-6, IL-8, IL-12, and interferon- γ (IFN- γ). Proinflammatory cytokines help in recruiting neutrophils to the affected lung tissue.⁸ Neutrophils are then activated and phagocytize and kill ingested bacteria by producing toxic-free oxygen radicals and bactericidal enzymes.⁶ Neutrophils also recruit monocytes, dendritic cells, and T-cells to site of infection, which can further amplify the inflammatory response.^{4,6,7} Once infection is controlled then anti-inflammatory cytokines, such as IL-10 and IL-4, will function

to restore homeostasis, modulate neutrophil apoptosis, and inhibit proinflammatory cytokine production.^{4,6,7} It is believed that an imbalance of the pro- and anti-inflammatory processes results in a deleterious effect leading to pulmonary endothelial barrier disruption, extravasation of protein-rich fluid and acute respiratory distress syndrome (ARDS).⁶

Glucocorticoids are important immune-modulating drugs and play an important role in the treatment of many chronic inflammatory disorders.^{4,7} They also play an important physiological role in the modulation of acute inflammation and have been tried in ICU patients with septic shock and ARDS with conflicting results.⁶ Infections in patients with adrenal insufficiency tends to be more severe and carries high mortality, suggesting that corticosteroids are important for a normal response in severe infections.⁴ Glucocorticoids play an important role in keeping the innate immune system ready to combat acute infections.^{4,7} In higher doses, corticosteroids inhibit production of various cytokines including IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, INF- γ , and TNF- α , thereby reducing their proinflammatory effect.^{4,7,9} With prolonged use, they also suppress the adaptive immune response and predispose to secondary infections.^{4,7,9} As a result of the complex role played by glucocorticoids in the host response to acute infections, the role of corticosteroids in infections has remained controversial.

STUDIES ON CORTICOSTEROIDS IN COMMUNITY-ACQUIRED PNEUMONIA

Patients with severe CAP might die despite early and adequate antibiotic treatment, probably due to an imbalanced or disproportionate local and systemic inflammatory response,^{10,11} that contributes to the impairment of alveolar gas exchange, sepsis, and end-organ dysfunction.^{1,3,5} Systemic adjunctive corticosteroid therapy attenuates the local and systemic inflammatory response.^{1,3,5} In humans, several small randomized controlled trials (RCTs) have been performed with the participants largely being hospitalized and

nonsevere CAP patients.³ The results of these trials have been negative or have demonstrated a reduction in the length of stay or in the time required to reach clinical stability but have not shown mortality benefit.³ Two important randomized clinical trials on corticosteroid in CAP have been recently published.

Blum et al. in 2015 investigated the effects of short-term prednisone versus placebo in patients admitted to hospital for CAP with the primary endpoint of time to clinical stability.⁵ This placebo-controlled double-blind study recruited patients admitted to seven tertiary-care hospitals in Switzerland between 2009 and 2014. A total of 802 patients were randomized within 24 hours of presentation to receive 50 mg of oral prednisone or placebo daily for 7 days in addition to standard treatment.⁵ The primary endpoint was time to clinical stability defined as stable vital signs 24 hours. Stable vital signs were temperature $\leq 37.8^{\circ}\text{C}$, heart rate ≤ 100 beats/min, spontaneous respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mmHg (≥ 100 mmHg for patients diagnosed with hypertension) without vasopressor support, return of mental status back to level before occurrence of CAP, ability for oral intake and partial arterial pressure of oxygen (PaO_2) ≥ 60 mmHg or pulse oximetry $\geq 90\%$ on room air.⁵

They found that a 7-day treatment with oral prednisone in patients with CAP led to a reduction in time to clinical stability by 1.4 days, an overall reduction of length of hospital stay by 1 day and to a reduction in duration of intravenous antibiotic treatment by 1 day.⁵ The prednisone group had a higher rate of hyperglycemia. However, there was no difference in mortality or length of ICU stay, or rates of recurrence of pneumonia or readmission to hospital in the two groups.⁵

In another study published in the same year, Torres et al. reported the results of a randomized double-blind placebo-controlled trial conducted in three Spanish hospitals.¹ The authors studied the effect of intravenous bolus of methylprednisolone (0.5 mg/kg every 12 hours for 5 days) versus placebo started within 36 hours of hospital admission.¹ This study differed from the Blum study, in that, it included only patients with severe pneumonia as defined by the modified American Thoracic Society criteria or risk class V by the pneumonia severity index. Patients also had to have C-reactive protein (CRP) level of >150 mg/L at admission. The primary endpoint in this study was a composite endpoint of early and late treatment failure.¹

Early treatment failure was defined as clinical deterioration within 72 hours of treatment (included development of shock, need for invasive mechanical ventilation not present at baseline or death). Late treatment failure was defined as radiographic progression (increase of $\geq 50\%$ of pulmonary infiltrates compared with baseline), persistence of severe respiratory failure (ratio of PaO_2 to fraction of inspired oxygen <200 mmHg, with respiratory rate ≥ 30 breaths/min in patients not intubated), development of shock, need for invasive mechanical ventilation not present at baseline

or death between 72 hours and 120 hours after treatment initiation. Interleukin-6, IL-8, IL-10, procalcitonin, and CRP levels were studied on days 1, 3, and 7.¹

Early treatment failure was comparable (10%) in both groups. Late failure was more common in the placebo group (25%) versus 3% in the steroid group ($p = 0.001$); this was mainly accounted for by radiographic progression (15 vs. 2%, $p = 0.007$). There was no difference in time to clinical stability, length of hospital and ICU stay, and inhospital mortality (15% with placebo vs. 10% in the steroid group, $p = 0.37$).¹

Both these studies had certain limitations. A large number of patients in the Blum study had mild pneumonia.^{5,12} In both studies, the recruitment period extended for several years (5 years in the Blum study and 8 years in the Torres study).^{1,5,13} In both studies, only 25–35% of patients with pneumonia admitted during this period were eligible for the study.^{1,5} A higher proportion of patients in the Torres study in the placebo group had shock at baseline and only about 25% of patients in both groups received macrolide antibiotics for pneumonia.¹³ Finally, both studies used surrogate endpoints rather than hard endpoints like mortality.^{1,5}

Implications of These Studies

Commenting on this study in an accompanying editorial, Wunderlink observed that the results of the Torres study suggest that the main effect of corticosteroids is to prevent radiological progression.¹³ Radiographic progression could occur due to uncontrolled pneumonia or due to development of ARDS.¹³ It is unlikely that corticosteroids will prevent worsening of infection. A more plausible explanation for radiological worsening may be due to a Jarisch-Herxheimer-like reaction, due to high concentrations of cytokines after initiation of antibiotics, possibly through release of endotoxin or other bacterial mediators in patients with a high bacterial load.¹³ Corticosteroids may block this phenomenon, equivalent to the use of corticosteroids in meningococcal meningitis.¹³ However, Wunderlink cautions that corticosteroids are not recommended for everyone with severe CAP as yet.¹³

A recent meta-analysis published after these two RCTs included six trials that included patients with severe CAP and six trials with less severe pneumonia.¹² The corticosteroid used included dexamethasone, prednisolone, prednisone, methylprednisolone, and hydrocortisone, while the duration of treatment ranged from 1 to 10 days.¹² This meta-analysis revealed that the risk ratio [95% confidence interval (CI)] for mortality for steroid treatment was 0.39 (0.2–0.77) for severe pneumonia, 1.0 (0.79–1.26) for less severe pneumonia. The relative risk (RR) for the need for mechanical ventilation was 0.54 (0.5–0.58) for severe and 0.18 (0.08–0.43) for less severe pneumonia and for development of ARDS 0.24 (0.1–0.56).¹² Steroids increased the risk of hyperglycemia (RR 1.49, CI 1.01–2.19), but not for gastrointestinal hemorrhage.¹²

Thus, current knowledge suggests that corticosteroids are useful in treating severe CAP and can help to decrease treatment failure and, possibly, mortality. However, it should be noted that many of the studies excluded patients with diabetes and those with H1N1 influenza pneumonia.¹³

CORTICOSTEROIDS IN H1N1 PNEUMONIA

Seasonal influenza is an acute respiratory disease that presents with sudden onset of high fever, upper respiratory tract symptoms, chills, myalgia, and gastrointestinal tract symptoms.¹⁴ Infection rarely induces symptoms of lower respiratory tract infections or severe lung injury. However, pandemic H1N1-infected patients present with fever, cough, and sore throat, and the most severe case rapidly develop bilateral pneumonia, severe ARDS, multiple organ failure, and death.¹⁴ It affects young individuals disproportionately and epidemiological studies suggest that pregnant women and obese patients were more susceptible to severe infection.¹⁴

In a retrospective analysis of data of 245 critically ill patients with H1N1 infection including 136 with ARDS from South Korea, Kim et al. reported an overall mortality was 43.6%.¹⁵ Patients who received steroids had higher mortality than patients who did not received steroids, even after propensity-adjusted analysis.¹⁵ Patients on steroids also had longer duration of mechanical ventilation and ICU stay, and more bacterial pneumonia or invasive fungal infections. Brun-Buisson et al. evaluated 208 patients with severe H1N1 infections and ARDS in a multicenter study in France; steroids were administered to 39.9%.¹⁶ After statistical techniques to adjust for differences in steroid-treated and nonsteroid-treated patients, steroid use was significantly associated with death; the effect was more pronounced in patients receiving early steroid therapy.¹⁶ A meta-analysis of nine cohort studies ($n = 1,405$) and 14 case-control studies ($n = 4,700$) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection with a risk ratio of 1.85 (95%, CI 1.46–2.33) for cohort studies and 4.22 (95%, CI 3.10–5.76) for case-control studies.¹⁷

The literature on corticosteroids in H1N1 infection thus shows that corticosteroids may actually increase overall mortality. Moreover, data also suggest that corticosteroids use is associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. It is possible that steroids may delay viral clearance and ultimately increase mortality. The role of steroids in other viral pneumonias (adenovirus, rhinovirus, and respiratory syncytial virus) has been less well studied.¹⁴

CORTICOSTEROIDS AND PNEUMONIA IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Inhaled corticosteroids are widely used in chronic obstructive pulmonary disease (COPD) and have been linked with an

increased risk of pneumonia, but do not increase mortality.¹⁸ The mechanisms of the increased risk of pneumonia with inhaled corticosteroid use remain undetermined, but might include impaired macrophage function, reduced bacterial adherence in the large airways and alteration of the pulmonary microbiome.¹⁸ Unproven strategies to reduce pneumonia risk in patients with COPD include discontinuing inhaled corticosteroids, reducing dose of inhaled corticosteroid, and changing type of inhaled corticosteroid.¹⁸

CORTICOSTEROIDS IN PNEUMOCYSTIS JIROVECI PNEUMONIA

Administration of corticosteroids within the first 72 hours of anti-*Pneumocystis jiroveci* treatment helps to prevent respiratory failure and death in AIDS patients. The standard approach is to use oral prednisone for 21 days (40 mg twice daily on days 1–5, 40 mg once daily on days 6–10 and 20 mg once daily on days 11–21).¹⁹ Patients who are severely ill or unable to take oral medication may be given an equivalent dosage of intravenous methylprednisolone (75% of the oral dose of prednisolone).¹⁹ The risk of reactivating tuberculosis (TB) or acquiring another infection appears to be minimal. A Cochrane review that included six RCTs showed that the risk ratio for overall mortality favoring adjunctive corticosteroids were 0.56 (95%, CI 0.32–0.98) at 1 month and 0.68 (95%, CI 0.50–0.94) at 3–4 months of follow-up. Only three trials provided data on the need for mechanical ventilation with a risk ratio of 0.38 (95%, CI 0.20–0.73) in favor of adjunctive corticosteroids.²⁰

CORTICOSTEROIDS IN TUBERCULOUS PNEUMONIA AND MILIARY TUBERCULOSIS

Adjunctive corticosteroid therapy can be used to relieve the severe systemic and respiratory morbidity of advanced pulmonary TB.^{21–23} Radiographically evident abnormalities, other than cavities, usually resolve faster with corticosteroid usage, although the benefit to the patient is uncertain and with no reduction in chronic respiratory disease or death.²¹ Given adequate chemotherapy with two or more effective antituberculous agents, adjunctive corticosteroid use does not appear to delay the time to conversion of sputum culture to negative.²¹ Dosages of prednisone of 40–60 mg/day (or equivalent) tapered over 4–8 weeks have been shown to be effective.²¹ Currently available data does not justify use of corticosteroids in all patients with pulmonary TB, but RCT in patients with pulmonary TB are warranted.²⁴

Associated adrenal insufficiency is an absolute indication for the administration of adjunctive corticosteroid treatment. However, adjunctive corticosteroid treatment is considered to be beneficial with TB meningitis, large pericardial effusion, miliary TB, immune reconstitution inflammatory syndrome, ARDS, and hemophagocytic syndrome.^{21–24}

CONCLUSION

Use of corticosteroids in CAP has been associated with decreased time to clinical stability and duration of hospitalization, but data from individual clinical trials with steroids do not suggest mortality benefit in CAP patients. However, a meta-analysis of all randomized trials suggests a mortality benefit in patients with severe CAP.

The main adverse effect observed in RCTs was hyperglycemia.

There is no consensus on which medication, dose, route or frequency is preferred.

Immunosuppressed patients, pregnant women, patients with recent gastrointestinal hemorrhage and diabetics were excluded in many trials and the benefit in this population is unproven.

Corticosteroid use in pneumonia due to influenza virus, especially the pandemic H1N1 strain, has been associated with increased mortality.

REFERENCES

1. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015;313(7):677-86.
2. Morgan AJ, Glossop AJ. Severe community acquired pneumonia. *BJA Educ*. 2016;16(5):167-72.
3. Confalonieri M, Kodric M, Satagujiana M, et al. To use or not to use corticosteroids for pneumonia? A clinician's perspective. *Monaldi Arch Chest Dis*. 2012;77(2):94-101.
4. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med*. 2005;353(16):1711-23.
5. Blum CA, Nigro N, Briel M, Schuetz P, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2015;385(9977):1511-8.
6. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-51.
7. Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore. *Trends Endocrinol Metab*. 2013;24(3):109-19.
8. Van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet*. 2009;374(9700):1543-56.
9. Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci*. 2013;34(9):518-30.
10. Antunes G, Evans SA, Lordan JL, et al. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J*. 2002;20(4):990-5.
11. Kellum JA, Kong L, Fink MP, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the genetic and inflammatory markers of sepsis (GenIMS) study. *Arch Intern Med*. 2007;167(15):1655-63.
12. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and meta-analysis. *Ann Intern Med*. 2015;163(7):519-28.
13. Wunderlink RG. Corticosteroids for severe community-acquired pneumonia: not for everyone. *JAMA*. 2015;313(7):673-4.
14. Nedel WL, Nora DG, Salluh JF, et al. Corticosteroids in severe influenza pneumonia: A critical appraisal. *World J Crit Care Med*. 2016;5(1):89-95.
15. Kim SH, Hong SB, Yun SC, et al. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am J Respir Crit Care Med*. 2011;183(9):1207-14.
16. Brun-Buisson C, Richard JC, Mercat A, et al. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2011;183(9):1200-6.
17. Zhang Y, Sun W, Svendsen ER, et al. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. *Crit Care*. 2015;19:46.
18. Finney L, Berry M, Singanayagam A, Elkin SL, et al. Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease. *Lancet Respir Med*. 2014;2(11):919-32.
19. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. (2016). Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medical Association of the Infectious Diseases Society of America. [online] Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. [Accessed September, 2016].
20. Briel M, Bucher H, Boscacci R, et al. Adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in patients with HIV-infection. *Cochrane Database Syst Rev*. 2006;3:CD006150.
21. Cunha BA. Pulmonary tuberculosis and steroids. *Chest*. 1995;107(6):1486-7.
22. Hagan G, Nathani N. Clinical review: Tuberculosis in the intensive care unit. *Crit Care*. 2013;17(5):240.
23. Critchley JA, Young F, Orton L, et al. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(3):223-37.
24. Thwaites GE. Adjunctive corticosteroids for all forms of tuberculosis? *Lancet Infect Dis*. 2013;13(3):186-8.

Extracorporeal Carbon Dioxide Removal/ Respiratory Dialysis: Future of Hypercapnic Respiratory Failure

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INTRODUCTION

Modern day critical care practice for respiratory distress mainly revolves around managing hypoxemic respiratory failure, but there are certain subset of patients who are admitted to intensive care unit (ICU) either for hypercapnic respiratory failure or develop it during their ventilator management for any other condition. These patients are either an acute exacerbation of chronic obstructive pulmonary disease (COPD) or patients developing "permissive hypercapnia" as a part of lung-protective ventilation (LPV) with low-tidal volume (LTV) strategy for acute respiratory distress syndrome (ARDS). The concept of LPV with LTV as per the ARDS Network (ARDSNet) protocol has been shown to be beneficial although associated with respiratory acidosis termed as permissive hypercapnia. The failure to implement LPV may be one of the reasons ICU mortality rates have remained unchanged.¹ When surveyed, healthcare providers reported that hypercapnia or its related effects were significant barriers to achieving LPV.²

Hypercapnia might have beneficial effects on oxygen delivery and attenuation of inflammation,³ but it can also harm the injured lung through immunosuppression and impaired pulmonary epithelial repair.^{4,5} Furthermore, hypercapnia perpetuates right heart failure⁶ by increasing pulmonary arterial pressure and leading to cor pulmonale. Hypercapnia is also undesirable in patients with elevated intracranial pressure. Thus the modern critical care practice in managing such patients is to balance the maximal use of LPV while avoiding the metabolic deleterious effects of hypercapnia. To achieve this goal, the use of extracorporeal carbon dioxide removal (ECCO₂R) devices has come in use.

PROBLEMS WITH HYPERCAPNIC ACIDOSIS

Cellular and Metabolic Effects

The theory of achieving LPV at the cost of hypercapnia has been practiced to avoid the ventilation-induced lung injury

induced by delivering high-tidal volumes. It was thought earlier that acidosis decreased the levels of proinflammatory mediators and decreased the levels of free radicals and cytokine-induced injury, but recent studies have shown that systemic metabolic acidosis may be beneficial but not hypercapnia-induced acidosis.⁷

Recent studies have confirmed that carbon dioxide (CO₂) can also act as a signaling molecule via pH-independent mechanisms, leading to deleterious effects in the lung. These effects include inhibition of cell membrane repair, impairment of alveolar fluid clearance, and suppression of innate immunity and host defense. There is also evidence that increased CO₂ levels impair the sodium, potassium adenosine triphosphatase function. These reports suggest that the beneficial effect of hypercapnia need to be relooked and we need to find ways to decrease the CO₂ accumulation.^{8,9}

Effect on Pulmonary Hemodynamics

Hypercapnia induces pulmonary vasoconstriction, which leads to increased pulmonary artery (PA) pressure in ARDS. This increased PA pressures leads to right ventricular failure leading to *de novo* cor pulmonale in patients with ARDS. Impaired right ventricle function in early stage ARDS may be underdiagnosed and yet it might be the harbinger of a downward spiral in the patient's condition.¹⁰

DEFINITION OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

It is a technique of partial respiratory support that achieves removal of CO₂ from the blood through a low blood flow (0.4–1 L/min) extracorporeal circuit, without significant effect on blood oxygenation. The major difference with extracorporeal membrane oxygenator (ECMO) is that in ECMO high blood flows of up to 3–7 L/min are used and there is significant improvement in oxygenation and CO₂ is also removed.

THE PRINCIPLE OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

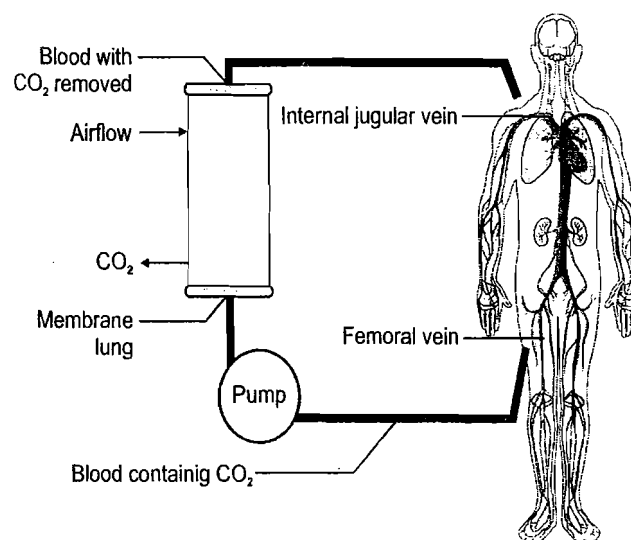
The basic principle of ECCO₂R is CO₂ removal without any major change in oxygenation. In its basic form, ECCO₂R consists of a drainage cannula placed in a large central vein, a pump, a membrane lung, and a return cannula (Fig. 1).

Blood is pumped through the membrane "lung" and CO₂ removal is facilitated by diffusion mechanism. A low flow of gas is given as a counter current to ensure the diffusion gradient favors CO₂ removal as these membranes are permeable to gases only and not to liquids.

Compared to ECMO, these devices work on low blood flows. Most of the CO₂ is transported as dissolved bicarbonate and displays linear kinetics without saturation. So, 1 L of blood carries more CO₂ compared to O₂ and 250 mL of CO₂ can be removed from <1 L of blood. However, in practice, the CO₂ removal depends on blood flow, sweep gas flow, and hemoglobin apart from the efficiency of the membrane "lung". The CO₂ removal displays a biphasic pattern with an initial rapid decline due to removal of dissolved CO₂ and then later a more steady removal of CO₂ released from dissolved bicarbonate. Through the ECCO₂R, a proportion of the total CO₂ production is cleared to allow reduction of mechanical ventilation (MV) and allow "lung rest".¹¹

THE MEMBRANE LUNG

The introduction of membrane lungs has made extracorporeal gas exchange more feasible. The concept of placing a barrier between blood and air began with the observation that gas exchange occurred across cellophane tubing in hemodialysis machines.^{12,13} This led to the development of membrane lungs consisting of gas permeable silicon-rubber mounted on a nylon mesh.¹⁴ The nylon mesh provided strength and avoided plasma leakage



CO₂, carbon dioxide.

FIG. 1: Scheme of extracorporeal carbon dioxide removal

from pinhole defects. Nowadays, the nonmicroporous poly-4-methyl-1-pentene has been used; it provides superior gas exchange, better biocompatibility, and lower resistance and is less susceptible to plasma leak.¹⁵

The modern membrane lungs achieve adequate gas exchange with surface areas of 1–3 m².

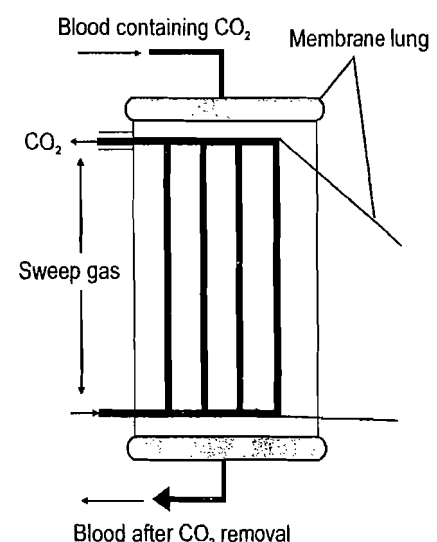
The amount of gas, which crosses the membranes, depends on the diffusion gradient, the membrane-blood contact time, and the membrane diffusion characteristics. The CO₂ diffusion gradient is determined by the CO₂ content of the blood and the air passing through the membrane lung as well as the speed of the airflow. Membrane-blood contact time is determined by membrane geometry. The addition of covalently bound heparin to membrane surfaces enhances the biocompatibility and gas exchange has been improved by arranging fibers into a complex mat and running blood on the outside¹⁶ (Fig. 2). This arrangement allows perpendicular blood flow to the fibers, improving mass transfer by reducing the diffusion path length compared to parallel flow.

TYPES OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL SYSTEMS

Traditionally, ECCO₂R systems can be categorized as arteriovenous ECCO₂R (AV-ECCO₂R) or venovenous ECCO₂R (VV-ECCO₂R) depending upon the site of access cannula.

Arteriovenous Carbon Dioxide Removal Devices

In AV-ECCO₂R, blood flow is achieved by an arterial pressure and the blood is returned in a venous system. The machine runs with a pumpless system as the force is generated by the arterial pressure of the patient. For this system, one cannula is placed in the femoral artery and the return cannula is placed in the femoral vein. The venous cannula is usually



CO₂, carbon dioxide.

FIG. 2: Membrane lung

larger than the arterial cannula. The major disadvantage is the placement of a large-bore arterial cannula, which can damage the arterial wall and can cause limb ischemia. In a reported series, distal ischemia occurs in 11–24% of cases.^{17,18} The risk of ischemia relates directly to the diameter of the arterial cannula. It is recommended that ultrasound of the artery is done prior to cannulation to ensure that the arterial lumen is at least 1.5 times the size of the arterial cannula.

Arteriovenous ECCO₂R is commercially available through Novalung and marketed as the interventional lung assist (iLA) membrane ventilator (Fig. 3).

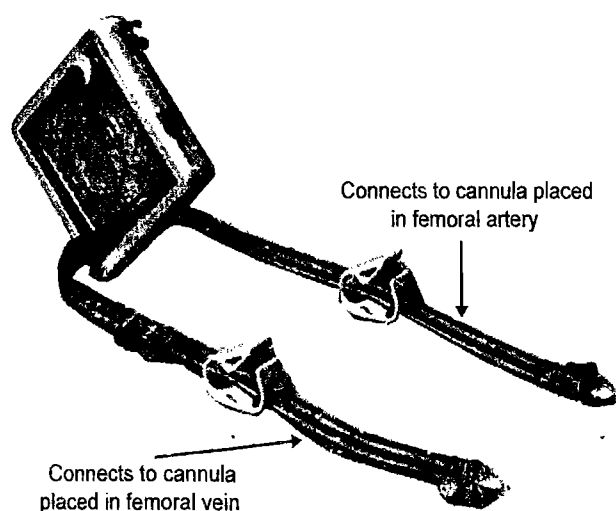
Novalung, utilizes a low resistance design allowing blood flow using the patient's own arteriovenous pressure gradient. As this is a pumpless system, the arteriovenous pressure gradient required would be >60 mmHg, which makes it an unsuitable modality in hemodynamically unstable patients.^{17,18}

Venovenous Carbon Dioxide Removal Devices

Venovenous devices require the insertion of cannula in two venous vessels and also require a mechanical pump to propel the blood through the extracorporeal circuit.

The cannula used for these devices are similar to the dialysis catheters. They are double lumen, wire reinforced, and coaxial cannula between 13 Fr and 19 Fr. The most common sites for insertion are internal jugular and femoral vein.¹⁹ The complications encountered in this approach are the same as for any other central line insertion like arterial puncture, hematoma at local site, false tract, and injury to the surrounding structures.²⁰

These cannulas may be inserted under ultrasound guidance as per the Seldinger technique. The aseptic precautions have to be maintained during the entire procedure of cannula insertion. As some of the catheters are not heparin coated, so systemic heparinization or flushing the catheters with heparinized saline is required at the time of cannula insertion.



130 FIG. 3: Interventional lung assist membrane ventilator

Pumps

All venovenous systems require a mechanical pump for propelling the blood. These mechanical pumps can be "roller or peristaltic" (older version) or the "rotary pumps". The roller pumps were cheap and reliable, but were more prone to hemolysis. To overcome these issues, the newer rotary pumps have been introduced.

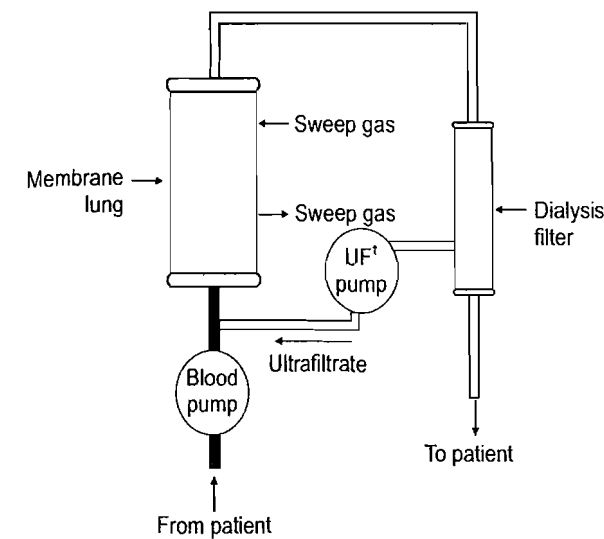
The rotary pumps can be of two types: (i) centrifugal and (ii) diagonal flow pumps. Centrifugal pumps use a radial-rotating impeller to create a suction vortex that draws blood into the center of the pump and spins it outwards, imparting centrifugal momentum, which is converted into driving pressure. In diagonal flow pumps, impeller design is a mix of radial and axial geometry. Centrifugal pumps tend to generate high pressures and low flows, whereas diagonal pumps produce both high flows and high pressures.²¹

These impellers are then connected to the drive shaft, which requires bearings to support the rotational movement. The movement of these typical bearings can seize when the coagulation debris deposits on them when the blood comes in contact with these bearings. To prevent this complication, some pumps use a seal to avoid this coating of coagulation debris and, hence, preventing the hindrance in rotary movement. Others have also tried to use biocompatible materials to construct such bearings. The recent and the most advanced form of impellers are surrounded by an electromagnetic field and thus avoiding the need for any drive shaft and bearings required for the rotary movement of this shaft; hence, preventing the generation of coagulation debris.

Decap Device

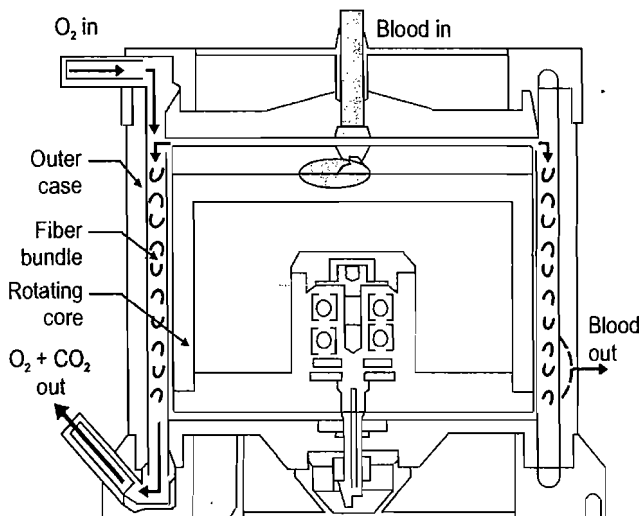
The Decap[®] ECCO₂R device is a modified renal replacement circuit incorporating a neonatal membrane lung coupled in series with a hemofilter. Venous access is achieved by insertion of a double-lumen 14 Fr hemodialysis catheter in a femoral vein under Seldinger technique (Fig. 4).

Blood flow is driven by a roller nonocclusive low-flow pump (maximum flow 450 mL/min) through a membrane lung connected to a fresh gas flow source delivering 100% oxygen at a constant rate of 4–6 L/min. Exiting the membrane lung, blood is driven to an hemofilter and the resulting plasmatic water is recirculated through the membrane lung by a peristaltic pump (0–155 mL/min). The circuit, including the membrane lung, is primed with saline at a volume that ranges between 140 mL and 160 mL. The new concept introduced by this newly designed technique is that the membrane lung and the hemofilter are coupled in series. The risk of air-bubble formation is reduced by this unique configuration of membrane lung in series with hemofilter, which is downstream and thus increasing the downstream resistance. This configuration also minimizes the need for heparin by diluting the blood entering the membrane



UF[†], ultrafiltrate.

FIG. 4: Decap system



O₂, oxygen; CO₂, carbon dioxide.

FIG. 5: Cross-section of Hemolung showing rotating core

lung by recirculating the plasmatic water separated by the hemofilter, hence, producing a performance enhancement of the extracorporeal device extracting the carbon dioxide dissolved in the plasmatic water separated by the hemofilter and recirculated through the membrane lung.²²

Hemolung (Fig. 5)

This device has been developed by Alung Technologies, where the membrane lung and centrifugal pump are combined together acting as one unit. In this device, the blood is drawn via a rotating impeller and the center of the core rotates to propel the blood toward the peripheral fibers. This process is named as active mixing. This creates disturbed blood flow and, hence, reducing diffusional resistance and increasing gas exchange. As a result, CO₂ removal is more efficient and achieved with a smaller membrane surface area and flows of

400–600 mL/min. So such a phenomenon can be achieved by a smaller double-lumen catheter. The smaller membrane surface area, siloxane coating for plasma resistance, and covalently bound heparin result in lower anticoagulation requirements.²³ Gas flow through the membrane lung is supplied under negative pressure, a safety feature preventing air embolism, if the membrane is disrupted.

CLINICAL EVIDENCE IN SUPPORT OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Regardless of whether the AV or VV approach is used, ECCO₂R devices can remove enough CO₂ to allow a 50% reduction in minute alveolar ventilation,²³ with significant reduction in partial arterial pressure of carbon dioxide (PaCO₂) and consequent reduction in PA pressure. This causes improvement in right ventricle-arterial coupling and, hence, reduction in incidence of cor pulmonale.

The studies have shown that a reduction in one-third of basal CO₂ production by the help of ECCO₂R devices at a low-flow rate can help in reduction of need of invasive ventilation and shifting the patient to noninvasive ventilation (NIV).^{24,25} More recent series in humans have demonstrated consistent evidence that PaCO₂ can be reduced and arterial pH due to respiratory acidosis improved using ECCO₂R.²⁶

CURRENT PRACTICE AND EVIDENCE OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

The current evidence of ECCO₂R is mostly based on observation studies or anecdotal case reports. There has been no randomized controlled trials (RCTs) on this modality. The interpretation of such studies is difficult as the inherent bias of selection and publication cannot be ruled out. Although ECCO₂R has not become standard of care in the critical care practice, but there is a large scope for its utility when it comes to prevention of hypercapnia and avoiding the deleterious effects of respiratory acidosis. The current evidence has been shown in the following subset of patients.

Acute Respiratory Distress Syndrome

Mechanical ventilation with LTV to limit the plateau pressures <30 mmHg to prevent ventilator-induced lung injury has become standard of care and has been shown to reduce mortality in ARDS patients. This ventilator strategy has been associated with increase in CO₂ levels termed as permissive hypercapnia leading to respiratory acidosis. This acidotic state been implicated to increase the pulmonary vascular resistance leading to RV failure and development of cor pulmonale. In these patients, the addition of ECCO₂R may allow control of hypercapnic respiratory acidosis and

facilitate ultraprotective ventilation, thereby limiting end-inspiratory lung stretch.

Morris et al. in a randomized trial showed that in patients with severe ARDS full ECCO₂R (meaning 100% CO₂ removal) compared to conventional MV had a lower mortality of 33% versus 42% for the control group.²⁷ In the prospective randomized "Xtravent-study", it was demonstrated that use of very LTV (3 mL/kg predicted body weight) combined with ECCO₂R with an arteriovenous configuration was safe and beneficial in patients with severe ARDS in terms of 28 and 60 ventilator-free days, but not mortality.²⁸

A systematic review of 14 studies (495 patients, 2 RCTs, and 12 observational studies) with equal split between AV- and VV-ECCO₂R showed that ECCO₂R was feasible, facilitating the use of LTV ventilation. Post hoc analysis was conducted and it showed an increase in ventilator-free days in patients with more severe ARDS, but the data failed to show any mortality benefit.²⁰

Looking at all these data, it seems reasonable to combine ECCO₂R with ultraprotective or LTV ventilation, when patient starts developing hypercapnia. Although there has been no evidence of mortality benefit, but we need more robust data to document it. We still do not know, which patient subset would benefit from ECCO₂R, but probably patients with severe ARDS with PaO₂/FiO₂ <100 mmHg should be benefited.

Chronic Obstructive Pulmonary Disease

Patients who present with acute exacerbation of COPD are initially managed with NIV failing which the need for invasive ventilation arises. Patients requiring invasive ventilation have weaning difficulty and the concern that the mortality for patients who require invasive MV after failing NIV has been shown to be higher than those, who are treated at the outset with invasive MV.¹¹

The rationale of avoiding invasive MV in this population is justified by the worse outcomes seen in patients who fail NIV. For this reason, ECCO₂R is being considered as an adjunctive therapy to NIV to facilitate the withdrawal of NIV, avoid intubation or facilitate early extubation. The feasibility of using VV-ECCO₂R for acute hypercapnic respiratory failure due to COPD exacerbations has been demonstrated in several cohort studies.^{29,30}

A recent study by Burki and colleagues reported the utility of VV-ECCO₂R using a double lumen catheter in COPD patients who were on NIV and the target was avoidance of invasive MV.³⁰ Within 6 hours of application, the pH and PaCO₂ decreased. A feasibility study was conducted by Abrams et al. to facilitate endotracheal extubation and weaning in patients with COPD who failed NIV. All patients were successfully extubated and mobilized within 24 hours of extubation.³¹

In summary, the arguments for ECCO₂R in exacerbations of COPD are compelling. In patients, who are failing NIV and

TABLE 1 Complications of ECCO₂R

Complications	VV-ECCO ₂ R	AV-ECCO ₂ R
Bleeding during Cannula insertion	0%	1.9%
Compartment syndrome	0%	1.9%
Ischaemia of limb	0%	5.9%
Malfunction of extracorporeal pump	5.6%	0%
Exchange membrane thrombosis	16.7%	Not reported
Thrombosis of cannula	16.7%	1.9%

AV-ECCO₂R, arteriovenous extracorporeal carbon dioxide removal; VV-ECCO₂R, venovenous extracorporeal carbon dioxide removal

who do not want intubation as well as palliative care, ECCO₂R seems a reasonable approach.³²

COMPLICATIONS WITH EXTRACORPOREAL CARBON DIOXIDE REMOVAL

The complications of both VV-ECCO₂R and AV-ECCO₂R should be looked separately due to different configuration and site of access cannula (Table 1).³³

CONCLUSION

Extracorporeal carbon dioxide removal is not a new concept, but it is an area of expanding interest. As evidence favoring low volume, low-pressure ventilation in ARDS is established the trend of applying these ventilation strategies in all critically ill patients will increase the use of extracorporeal modalities for CO₂ removal.

Simpler more efficient ECCO₂R devices requiring lower blood flow rates and smaller access cannulas promise to improve safety and ease of use. Newer novel concept, such as the Decap, can serve the dual purpose of renal support and ECCO₂R. One needs to be aware of the potential complications of ECCO₂R when considering patients for extracorporeal support.

Although these devices have still not been accepted as standard of care in management of respiratory acidosis in patients with ARDS or acute exacerbation of COPD, familiarity with devices already available can change our approach to ARDS.

REFERENCES

1. Kalhan R, Mikkelsen M, Dedhiya P, et al. Underuse of lung protective ventilation: Analysis of potential factors to explain physician behavior. *Crit Care Med*. 2006;34(2):300-6.
2. Rubenfeld GD, Cooper C, Carter G, et al. Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med*. 2004;32(6):1289-93.
3. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Crit Care*. 2010;14(2):220.
4. O'Croinin DF, Nichol AD, Hopkins N, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. *Crit Care Med*. 2008;36(7):2128-35.

5. O'Toole D, Hassett P, Contreras M, et al. Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. *Thorax*. 2009;64(11):976-82.
6. Mekontso Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med*. 2009;35(11):1850-8.
7. Nichol AD, O'Cronin DF, Howell K, et al. Infection-induced lung injury is worsened after renal buffering of hypercapnic acidosis. *Crit Care Med*. 2009;37(11):2953-61.
8. Vadasz I, Hubmayr RD, Nin N, et al. Hypercapnia: a nonpermissive environment for the lung. *Am J Respir Cell Mol Biol*. 2012;46(4):417-21.
9. Briva A, Vadasz I, Lecuona E, et al. High CO₂ levels impair alveolar epithelial function independently of pH. *PLoS One*. 2007;2(11):e1238.
10. Lheritier G, Legras A, Caille A, et al. Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. *Intensive Care Med*. 2013;39(10):1734-42.
11. Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO₂ removal systems in mechanical ventilation. *Curr Opin Crit Care*. 2012;18(1):93-8.
12. Cove ME, MacLaren G, Federspiel WJ, et al. Bench to bedside review: extracorporeal carbon dioxide removal, past present and future. *Crit Care*. 2012;16(5):232.
13. Kolff WJ, Berk HT, ter Welle M, et al. The artificial kidney: a dialyser with a great area. 1944. *J Am Soc Nephrol*. 1997;8(12):1959-65.
14. Bramson ML, Osborn JJ, Main FB, et al. A new disposable membrane oxygenator with integral heat exchange. *J Thorac Cardiovasc Surg*. 1965;50:391-400.
15. Toomasian JM, Schreiner RJ, Meyer DE, et al. A polymethylpentene fiber gas exchanger for long-term extracorporeal life support. *ASAIO J*. 2005;51(4):390-7.
16. Gaylor JD. Membrane oxygenators: current developments in design and application. *J Biomed Eng*. 1988;10(6):541-7.
17. Bein T, Weber F, Philipp A, Prasser C, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med*. 2006;34(5):1372-7.
18. Zimmermann M, Bein T, Arlt M, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care*. 2009;13(1):R10.
19. Ventetuolo CE, Muratore CS. Extracorporeal life support in critically ill adults. *Am J Respir Crit Care Med*. 2014;190(5):497-508.
20. Fitzgerald M, Millar J, Blackwood B, et al. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care*. 2014;18(3):222.
21. Reul HM, Akdis M. Blood pumps for circulatory support. *Perfusion*. 2000;15(4):295-311.
22. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbondioxide removal. *Anesthesiology*. 2009;111(4):826-35.
23. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO₂ removal. *Crit Care Med*. 2011;39(6):1382-7.
24. Marcolin R, Mascheroni D, Pesenti A, et al. Ventilatory impact of partial extracorporeal CO₂ removal (PECOR) in ARF patients. *ASAIO Trans*. 1986;32(1):508-10.
25. Pesenti A, Rossi GP, Pelosi P, et al. Percutaneous extracorporeal CO₂ removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. *Anesthesiology*. 1990;72(3):571-3.
26. Health Quality Ontario. Extracorporeal lung support technologies—bridge to recovery and bridge to lung transplantation in adult patients: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2010;10(5):1-47.
27. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(2):295-305.
28. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy (≈ 3 ml/kg) combined with extracorporeal CO₂ removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized XlraVent-study. *Intensive Care Med*. 2013;39(5):847-56.
29. Roncon-Albuquerque R Jr, Carona G, et al. Venovenous extracorporeal CO₂ removal for early extubation in COPD exacerbations requiring invasive mechanical ventilation. *Intensive Care Med*. 2014;40:1969-70.
30. Burki NK, Mani RK, Herth FJ, et al. A novel extracorporeal CO₂ removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest*. 2013;143(3):678-86.
31. Abrams DC, Brenner K, Burkart KM, et al. Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2013;10(4):307-14.
32. Roncon-Albuquerque R Jr, Brodie D. Extracorporeal CO₂ removal in severe chronic obstructive pulmonary disease exacerbations: a work in progress. *Crit Care Med*. 2015;43(3):e102-3.
33. Baker A, Richardson D, Craig G. Extracorporeal carbon dioxide removal (ECCO₂R) in respiratory failure: an overview, and where next?. *Journal of Intensive Care Society*. 2012;13(3):232-7.

Extracorporeal Membrane Oxygenation in Acute Hypoxemic Respiratory Failure: Current Status in India

Sandeep Dewan, Munish Chauhan, Madhur Arora

INTRODUCTION

The use of adult Extracorporeal Life Support (ECLS) for hypoxic respiratory failures is a fairly recent addition to the armamentarium of an intensivist. Its usage picked up pace worldwide after the 2009 H1N1 epidemic. Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial¹ published in 2009 showed the evidence that these patient have better survival, if managed on extracorporeal membrane oxygenation (ECMO). The evidence²⁻⁵ related to its indications and contraindications has been growing and so also its outcomes. It has led to the development of uniform criteria²⁻⁶ for institution of the modality and has been aided by better prediction models like Murray score^{1,7} (for Lung Injury) or new definitions [Berlin definition acute respiratory distress syndrome (ARDS)].⁸ Newer models to predict outcomes on respiratory ECMO are also available [Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score]⁹ The same cannot be said about the modality in Indian intensive care units (ICUs). Very few centers actually use it in a protocolized manner or have handled a great volume of cases. The data is scarce regarding the number of ECMO runs in Indian centers. This article will discuss the basics of this modality and the current status in India, emphasizing the need to look at it with greater perspective as a lifesaving modality but in an organized manner.

TYPES OF EXTRACORPOREAL MEMBRANE OXYGENATION^{4,5} (TABLE 1)

The two basic types of ECMO are venoarterial (VA) and venovenous (VV) (Figs 1 and 2). This terminology describes the direction of blood flow. The outflow is always venous, but the inflow can be arterial (VA) or venous (VV). Outflow of blood in VA and VV ECMO is from the right atrium through a catheter placed through the femoral veins or right internal

TABLE 1 Venovenous extracorporeal membrane oxygenation versus venoarterial extracorporeal membrane oxygenation

Venovenous	Venoarterial
<ul style="list-style-type: none"> Only supports lungs Only venous cannulation ECMO circuit is in series to heart and lungs Minor cardiac implications: <ul style="list-style-type: none"> Limited to a closed loop on venous side No effect on RV/LV pre- and afterload Not of use in RV failure RV afterload may decrease sometimes; improves oxygenation 	<ul style="list-style-type: none"> Both heart and lung supported Both venous and arterial cannulation ECMO circuit is in parallel to heart and lungs Decreases the RV preload and thus pulmonary circulation Increases LV afterload <ul style="list-style-type: none"> LV stunning Can be used in RV failure Decreases arterial Pulse pressure: non Pulsatile flow and its implications

RV, right ventricle; LV, left ventricle; ECMO, extracorporeal membrane oxygenation.

jugular vein. In older patients, other venous sites have been used.

- Venoarterial ECMO takes deoxygenated blood from a central vein or the right atrium commonly via the femoral vein or internal jugular, pumps it past the oxygenator, and then returns the oxygenated blood, under pressure, to the arterial side of the circulation, typically to the aorta via the femoral artery. This form of ECMO partially supports the cardiac output as the flow through the ECMO circuit is in addition to the normal cardiac output. It is in parallel to native circulation
- Venovenous ECMO takes blood from a large vein (mostly femoral) and returns oxygenated blood back to a large vein (mostly jugular). Venovenous ECMO does not support the circulation. It takes over partially the lung function and acts in series to native circulation.

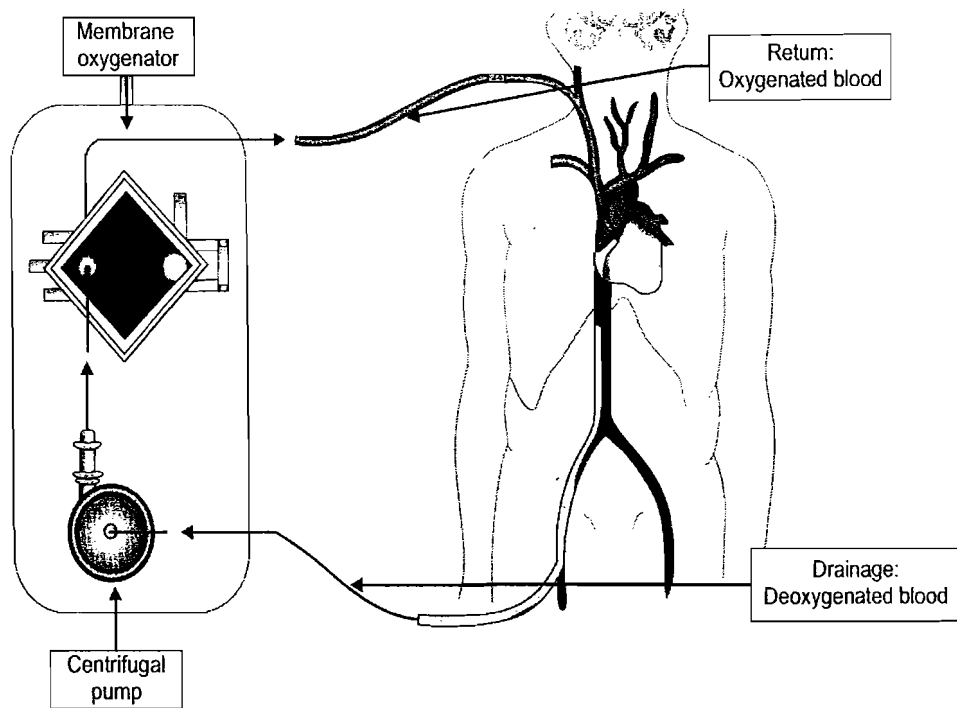


FIG. 1: Simplified venovenous extracorporeal membrane oxygenation circuit (Femoral-Jugular)

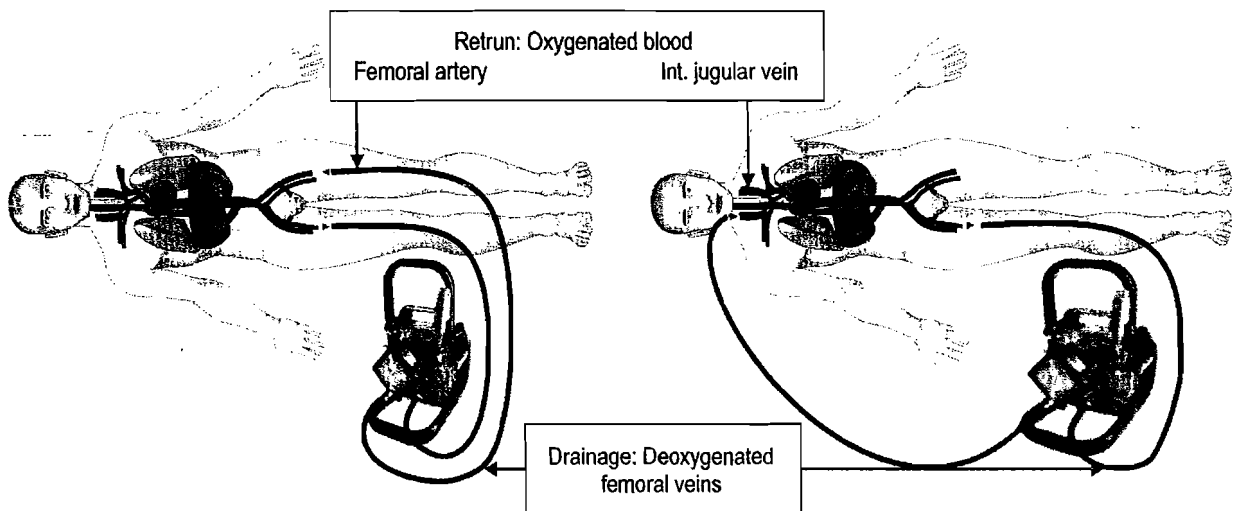


FIG. 2: Configurations of venovenous and venoarterial extracorporeal membrane oxygenation circuit

INDICATIONS²⁻⁶

Extracorporeal Membrane Oxygenation Indications for Respiratory Support

Both VVECMO and VA ECMO can be used as a rescue therapy in acute respiratory failure to buy time and allow the lungs to heal in the meantime by maintaining the physiology as near normal as possible. Extracorporeal membrane oxygenation is used to provide oxygenation and CO₂ removal, or both while the lungs and the primary disease recover, or as a bridge to transplant in case of end-stage lung disease.

- Severe ARDS:
 - Severe bacterial or viral pneumonia
 - Aspiration syndromes
- Extracorporeal assistance to provide lung rest:
 - Airway obstruction
 - Pulmonary contusion
 - Smoke inhalation
- Lung transplant:
 - Primary graft failure after lung transplantation
 - Bridge-to-lung transplant
- Lung hyperinflation:
 - Status asthmaticus

- Pulmonary hemorrhage or massive hemoptysis
- Congenital diaphragmatic hernia and meconium aspiration.

Extracorporeal Membrane Oxygenation for Cardiac Support (Venoarterial ECMO Only)

Refractory low-cardiac output (cardiac index <2 L/min/m²) and hypotension (systolic blood pressure <90 mmHg) despite adequate intravascular volume, high-dose inotropic agents and with/without intra-aortic balloon pump.

- Cardiogenic shock:
 - Acute coronary syndrome
 - Refractory cardiac arrhythmias
 - Sepsis with profound cardiac depression
 - Drug overdose/toxicity with profound cardiac depression
 - Myocarditis
 - Pulmonary embolism (PE)
 - Isolated cardiac trauma
- Postcardiotomy: Inability to wean from cardiopulmonary bypass after cardiac surgery
- Post-heart transplant: Primary graft failure after heart or heart-lung transplantation
- Chronic cardiomyopathy:
 - As a bridge to longer term ventricular assist device (VAD) support
- Periprocedural support for high-risk percutaneous cardiac interventions
- Bridge to transplant.

Contraindications to

Extracorporeal Membrane Oxygenation^{4,5,10}

Absolute

Among these futile treatments without exit strategy in case of:

- Unrecoverable heart and not a candidate for transplant or destination therapy of VAD support
- Disseminated malignancy
- Known severe brain injury
- Unwitnessed cardiac arrest
- Prolonged cardiopulmonary resuscitation (CPR) without adequate tissue perfusion
- Unrepaired aortic dissection
- Severe aortic regurgitation
- Severe chronic organ dysfunction (emphysema, cirrhosis and renal failure)
- Compliance (financial, cognitive, psychiatric, or social limitations in patient without social support)
- Peripheral vascular disease is contraindicated in peripheral VA ECMO
- Venovenous ECMO is contraindicated, if the patient is on mechanical ventilation at high settings ($\text{FiO}_2 >0.9$, $\text{P}_{\text{plat}} >30$) for 7 days or more

- Venovenous ECMO is contraindicated in cardiogenic failure and in severe chronic pulmonary hypertension (mean pulmonary artery pressure >50 mmHg).

Relative

- Contraindication for anticoagulation, advanced age, and obesity.

COMPLICATIONS OF EXTRACORPOREAL MEMBRANE OXYGENATION^{5,8,9}

Extracorporeal membrane oxygenation is fraught with complications, minor-to-major, related to the modality or the primary disease itself. It is generally accepted that respiratory VV ECMO has less complications than cardiac VA ECMO, the highest rate being for extra-CPR. Most frequent is hemorrhage,¹¹ especially surgical site and others, some requiring even surgery (VA 34%; VV 17%).¹² Forty three percent of ECMO deaths are attributed to intracranial hemorrhage.¹³ Thromboembolism is another issue, more dangerous in VA ECMO as it will directly compromise systemic circulation.

Cannulation is one factor that makes VV safer and easier as it does not involve breaching the arterial system. These include vessel perforation causing hemorrhage, arterial dissection, distal limb ischemia, and incorrect location (e.g., venous cannula within the artery). Though these complications are rare ($<5\%$), they can be troublesome. Another problem unique to cardiac ECMO is "Harlequin syndrome" or "North-South syndrome". It occurs because of a competitive flow in the aorta (ECMO vs. heart) leading to deoxygenated blood supplying the upper body (blue head) and hyperoxygenated blood to the lower body (red legs).^{14,15} The risk of left ventricle (LV) overload leading to stunning/failure is a real threat with VA ECMO.

Thus, it is but natural that the preferred ECMO configuration to be used for acute respiratory failure is VV; unless associated with severe cardiogenic shock. Moreover, it is not possible to rest the lungs by decreasing driving pressures, tidal volume, plateau pressures, etc. if VA ECMO is used.

EXTRACORPOREAL MEMBRANE OXYGENATION IN ACUTE RESPIRATORY FAILURE: WHEN TO CONSIDER^{1,6,10}

- As per Extracorporeal Life Support Organization (ELSO) guidelines, in hypoxic respiratory failure due to any cause (primary or secondary), ECLS should be considered when the risk of mortality is $\geq 50\%$, and is indicated when the risk of mortality is $\geq 80\%$
 - About 50% mortality risk is associated with a partial arterial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <150 on $\text{FiO}_2 >90\%$ and/or Murray score 2-3

- About 80% mortality risk is associated with a $\text{PaO}_2/\text{FiO}_2 < 100$ on $\text{FiO}_2 > 90\%$ and/or Murray score 3–4 despite optimal care for 6 hours or more
- Carbon dioxide retention on mechanical ventilation despite high P_{plat} ($> 30 \text{ cm H}_2\text{O}$)
- Severe air leak syndromes
- Need for intubation in a patient on lung transplant list
- Immediate cardiac or respiratory collapse (PE, blocked airway, and unresponsive to optimal care).

to other modalities and some unique to ECMO. Lack of resources, financial limitations, awareness, expertise and data sharing are the prominent few.

Cardiac ECMO in the form of postcardiac surgery support has been available and in use in India for some time now, but the advent of respiratory ECMO in India was facilitated by the 2009 H1N1 epidemic in parallel to the rest of the world, albeit at a much smaller scale.

EXTRACORPOREAL MEMBRANE OXYGENATION FOR ACUTE RESPIRATORY FAILURE: INDIAN SCENARIO

As with several other novel techniques, the progression of ECMO in India has faced several hurdles, some common

EXTRACORPOREAL LIFE SUPPORT ORGANIZATION CENTERS¹⁶

The ELSO is the umbrella organization, which brings all the ECMO centers across the world (Fig. 3) together with the purpose of knowledge disbursement and data sharing (Fig. 4). India comes under the South and West Asia Chapter

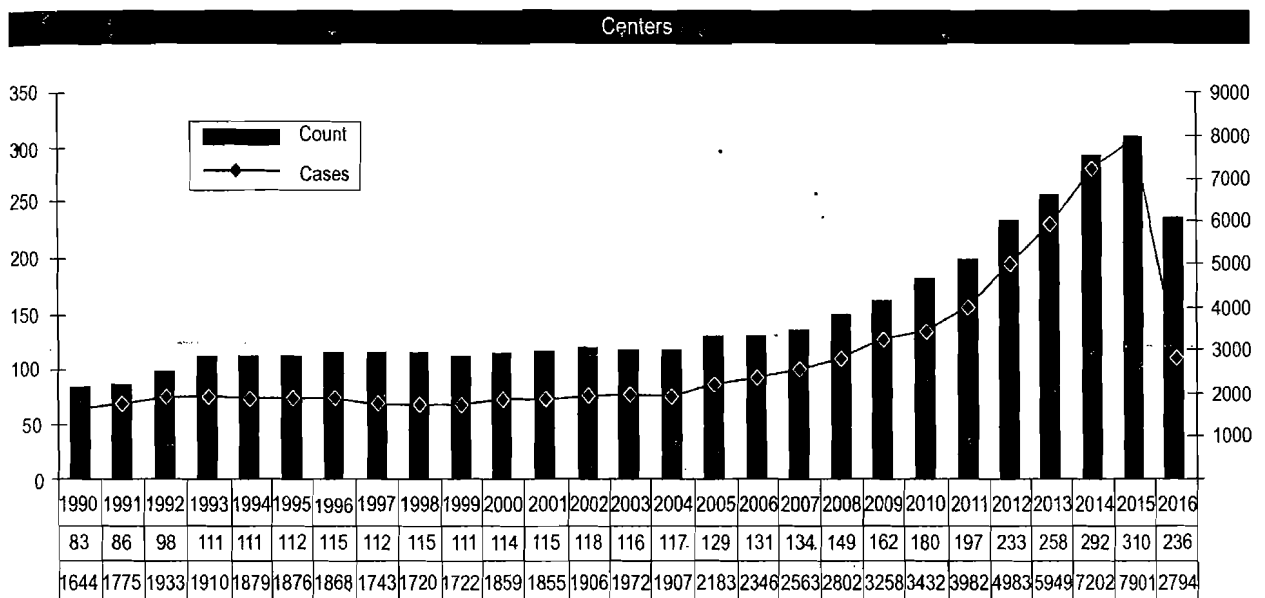


FIG. 3: Centers registered with Extracorporeal Life Support Organization till July, 2016 .

Courtesy: Extracorporeal Life Support Organization Registry, 2016.

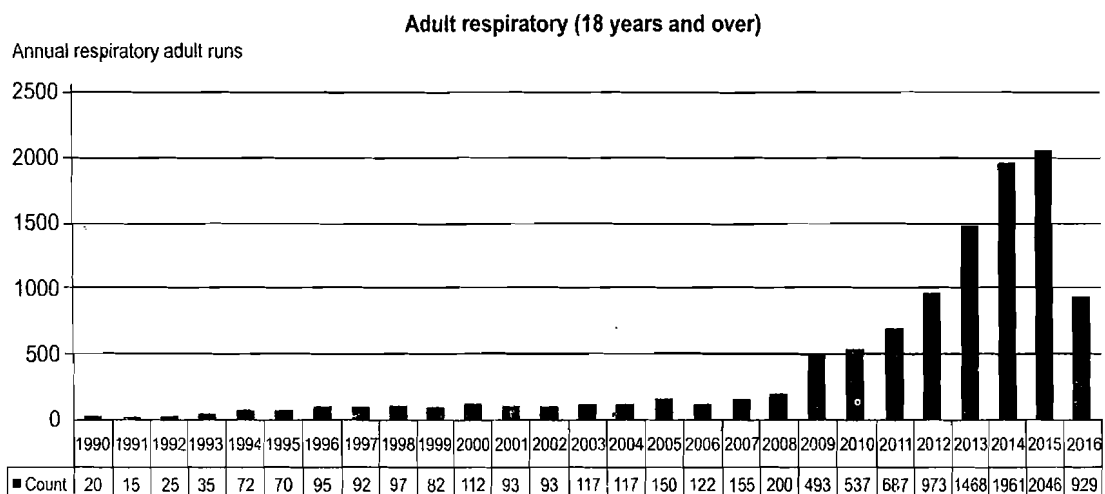


FIG. 4: Respiratory extracorporeal membrane oxygenation runs: annual distribution

Courtesy: Extracorporeal Life Support Organization Registry, July, 2016.

of ELSO (SWAC-ELSO). Till date, all across India, 11 centers are members of ELSO, which share their data with the organization. Details as per the ELSO member list are below:

- Bangalore
 - Fortis Hospitals Limited
 - Manipal Hospital
 - Narayana Institute of Cardiac Sciences
- Chennai
 - Apollo Hospital
- Gurgaon
 - Fortis Memorial Research Institute (FMRI)
- Ludhiana
 - Dayanand Medical College
- Mumbai
 - Riddhi Vinayak Critical Care and Cardiac Centre (RVCC)
- New Delhi
 - Max Super Speciality Hospital
 - The Simulation Society (TSS) at AIIMS
- Secunderabad
 - Krishna Institute of Medical Sciences
- Surat
 - Unique Hospital.

Considering the size and population of our country, and healthcare scenario, it is imperative that these numbers should be growing over time. Many centers are doing really good work on ECMO, e.g., Fortis Malar in heart failures, transplants and left ventricular assist device (LVADs); RVCC Mumbai who had pioneered the concept of ECMO in India and continue to do large numbers. They also hold the annual ECMO Conference in India. In North India, AIIMS continues to do ECMOs in postcardiac surgery cases, and Max Super

Speciality Hospital also has a well-run dedicated ECMO program.

Since there is no published data on ECMO from any of the above mentioned centers, the data of FMRI, Gurgaon, is being shared. The data has been shared with and ratified by the ELSO,¹⁶ the Michigan, United States-based body, which maintains and analyses the world's largest data registry (Table 2).

TABLE 2 International summary: overall outcomes

Overall outcomes					
	Total patients	Survived ECLS	Survived to DC or transfer		
Neonatal					
Respiratory	29,153	24,488	84%	21,545	74%
Cardiac	6,475	4,028	62%	2,695	42%
ECPR	1,336	859	64%	547	41%
Pediatric					
Respiratory	7,552	5,036	67%	4,371	58%
Cardiac	8,374	5,594	67%	4,265	51%
ECPR	2,996	1,645	55%	1,232	41%
Adult					
Respiratory	10,601	6,997	66%	6,121	58%
Cardiac	9,025	5,082	56%	3,721	41%
ECPR	2,885	1,137	39%	848	29%
Total	78,397	54,866	70%	45,345	58%

ECLS, extracorporeal life support, E-CPR, extra-cardiopulmonary resuscitation.
Courtesy: Extracorporeal Life Support Organization data Registry, July, 2016

Center statistics

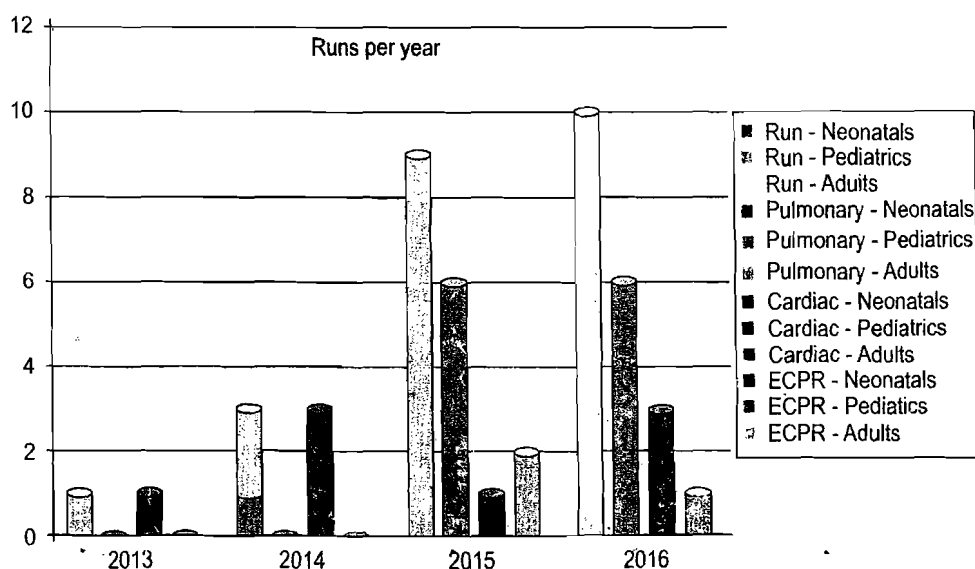
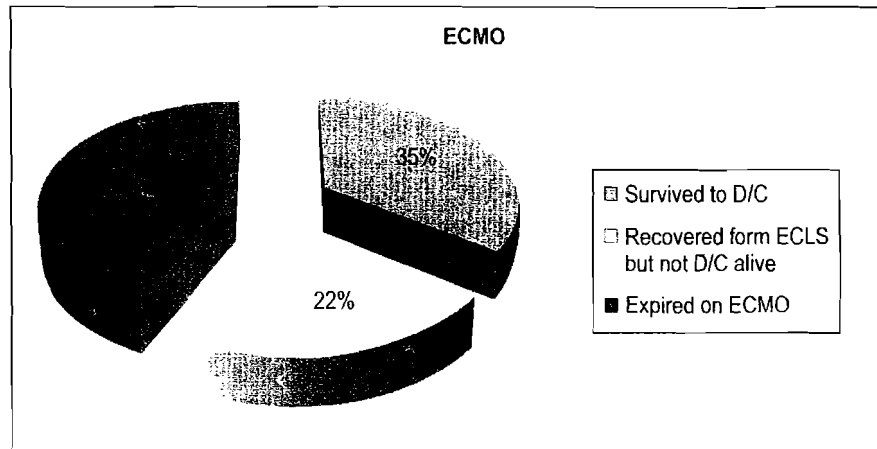


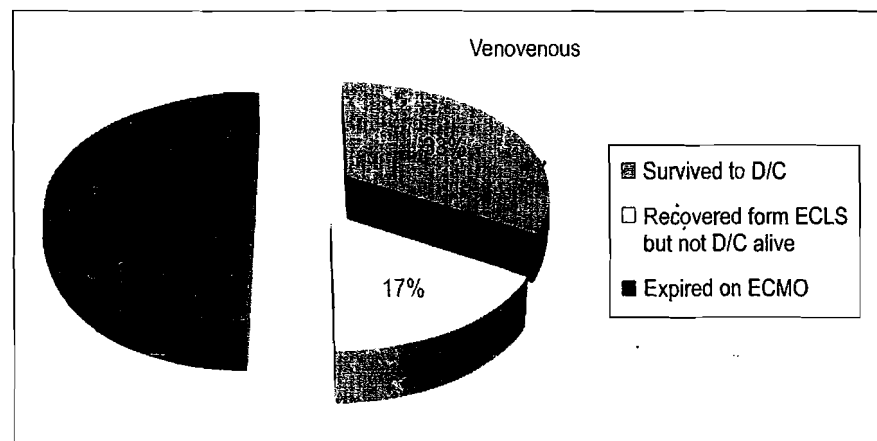
FIG. 5: Data of extracorporeal membrane oxygenation runs at Fortis Memorial Research Institute, Gurgaon, since program inception

Courtesy: Extracorporeal Life Support Organization Registry, Centre Statistics November, 2016



ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.

FIG. 6: Overall extracorporeal membrane oxygenation runs at Fortis Memorial Research Institute, Gurgaon (latest till November, 2016)



ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.

FIG. 7: Venovenous extracorporeal membrane oxygenation runs at Fortis Memorial Research Institute, Gurgaon (latest till November, 2016)

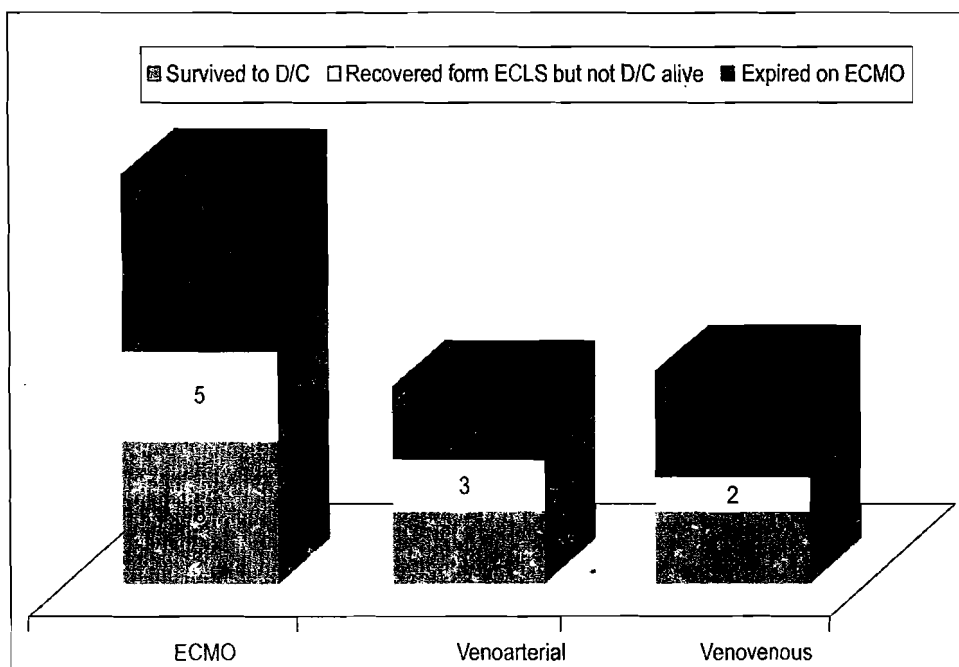


FIG. 8: Case breakup: extracorporeal membrane oxygenation runs at Fortis Memorial Research Institute, Gurgaon (latest till November, 2016)

ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation

Data from Fortis Memorial Research Institute, Gurgaon (Center ID 501)

The center started its ECMO program in December 2013 and has been sharing its data with ELSO as its member since March 2016. Since, then 23 ECMO (VA + VV) runs have been carried out at the center (Fig. 5) with a successful trial off in 13 (56.52%) of them after adequate recovery. Eight of the 13 (61.54%) were discharged alive. Overall survival was 34.78% (Table 3 and Fig. 6).

TABLE 3 Overall outcomes at Fortis Memorial Research Institute, Gurgaon (Extracorporeal Life Support Organization Center 501)

Overall outcomes					
	Total patients	Survived ECLS		Survived to DC or transfer	
Pediatric					
Cardiac	1	1	100%	1	100%
Adult					
Respiratory	12	6	50%	4	33.3%
Cardiac	7	4	57%	2	29%
ECPR	3	2	66.67%	1	33.3%
Total	23	13	56.5%	8	34.78%

ECLS, extracorporeal life support; E-CPR, extra-cardiopulmonary resuscitation. Courtesy: Extracorporeal Life Support Organization Registry, 2016.

If only respiratory ECMO runs are considered, 12 cases were VV ECMO. Six (50%) of them survived from ECMO, 4 (66.67%) of them were discharged alive. Overall survival was 33.33% (Figs 7 and 8). None of the mortalities were related to ECMO. They were related to the primary disease itself or acquired sepsis.

The fact that complications are common with ECMO is a widely accepted fact, less so with VV ECMO and the authors did face a few. Cannula site bleed was faced in one patient requiring surgical intervention. Infectious complications were the most common occurring in up to 41.67% cases. These infections were not per se related to the ECMO each time but general ICU infections. Other common but less troubling problems were thrombocytopenia and subclinical hemolysis. The oxygenator needed a change in one case due to persistent candidemia. None of the cases required discontinuation due to ECMO complications. The indications for respiratory ECMO were viral pneumonias (non-H1N1)—3 cases and acute worsening of acute interstitial lung disease (ILD/BOOP)—3 cases. Secondary ARDS accounted for four cases and diffuse alveolar hemorrhage for two cases. The average runtime on respiratory ECMO was 251.25 hours with the longest runtime of 342.5 hours (Table 4).

The rate of negative consent for ECMO is fairly high (40% since January–October, 2016), which the authors are sure exhibits the trend in other centers also, compounded by the lack of funds or absence of health insurance. As cost is a major-limiting factor, a low cost circuit can be assembled for shorter runs, affordability issues or cases with unpredictable outcomes, e.g., extra-CPR.

TABLE 4 Details of adult respiratory extracorporeal membrane oxygenation runs at Fortis Memorial Research Institute, Gurgaon (Extracorporeal Life Support Organization Center 501)

Adult Respiratory (18 years and over)					
Adult respiratory runs by diagnosis					
	Total runs	Average run time	Longest run time	No. survived	Survived (%)
Viral pneumonia	3	177	342.5	1	33.3
ARDS not postop/trauma	4	129	150	1	25
Acute resp failure, non-ARDS	1	90	90	0	0
Other	4	160	224	2	50
Run time in hours. Survived = survival to discharge or transfer based on number of runs					
Adult respiratory support mode details					
	Total runs	Average run time	Longest run time	No. survived	Survived (%)
Venovenous	12	251.25	342.5	4	33.3
Run time in hours. Survived = survival to discharge or transfer based on number of runs					
Adult respiratory complications					
	No. reported	% reported	No. survived	Survived (%)	
Mechanical: Cannula problems	1	8.3%	0	0	
Infectious: Culture proven infection (see infections)	5	41.67%	2	40	

ARDS, acute respiratory distress syndrome.

Courtesy: Extracorporeal Life Support Organization data Registry, 2016

SETTING-UP AN EXTRACORPOREAL MEMBRANE OXYGENATION PROGRAM (ADAPTED FROM THE ELSO GUIDELINES FOR ECMO CENTERS, MARCH 2014)¹⁷

There is ample evidence to suggest that better outcomes are achieved in high volume centers with rapid turnover of patients. Constant upgradation and improvement of skills is the key for good results. The way forward is regular training, audits, simulations, etc. especially in low-volume centers; and is the standard-of-care as per ELSO. Extracorporeal membrane oxygenation is a multidisciplinary care modality, and needs intensivists, vascular/cardiac surgeons, technicians, perfusionists, trained nurses, noninvasive cardiologists for echocardiographic guidance in the form of regular assessment of cardiac function, etc. The ELSO has published guidance on establishing ECMO centers, last upgraded in March 2014. As with any guidelines, these should be viewed as guiding parameters only as local factors in India vary hugely from the Western world.

- Extracorporeal membrane oxygenation centers should be located in tertiary centers with a tertiary level neonatal intensive care unit, pediatric intensive care unit and/or adult intensive care unit
- Extracorporeal membrane oxygenation centers should be located in geographic areas that can support a minimum of six ECMO patients per center per year. The cost effectiveness of providing fewer than six cases per year combined with the loss, or lack of clinical expertise associated with treating fewer than this number of patients per year should be taken into account when developing a new program
- Extracorporeal membrane oxygenation centers should be actively involved in the ELSO including participation in the ELSO registry.

General Structure and Staffing

The ECMO center should be located in a tertiary level intensive care unit with the following components:

- There should be a single physician ECMO program director with responsibility for the overall operation of the center. While there may be several associate directors with specific interests or focus in limited areas of ECMO care, the primary medical director should be responsible for assuring appropriate specialist training and performance, directing quality improvement meetings and projects, assuring proper and valid data submission to ELSO, and should also be responsible for the credentialing of other physicians who care for ECMO patients or who manage the ECMO circuit
- There should be an ECMO coordinator with responsibility for the supervision and training of the technical

staff, maintenance of equipment and collection of patient data

- The multidisciplinary ECMO team should have quality assurance review procedures in place for annual ECMO evaluation internally
- Formal policy and procedures outlining the indications and contraindications for ECMO, clinical management of the ECMO patient, maintenance of equipment, termination of ECMO therapy, and follow-up of the ECMO patient should be available for review
- Appropriate laboratory space for training and continuing medical education should be available.

The guidelines further highlights the recommendations related to staffing, training, research, data collection, and physical facilities and maintenance of equipment, which can be accessed on the ELSO website.

Barriers to the Development of Extracorporeal Membrane Oxygenation in India

Paucity of Trained Personnel

A recognized and protocolized ECMO training program for physicians, nurses, and technicians is almost nonexistent at this time in our country. Initiating and managing an ECMO patient different and all members need to be highly trained. A structured course at all levels is needed. At present, only two major ECMO conferences and trainings are held annually, one by the ECMO Society of India and other at the authors' center, FMRI, Gurgaon. Trained personnel go a long way in improving the outcomes and bringing down untoward incidences.^{18,19}

Learning Curve

As with any novel technique, ECMO also has its own natural learning curve.²⁰ And understandably, mortality and complication rates will definitely be higher in earlier stages and improve as the team gains experience. At present, several centers in India are in initial stages of developing their program; add to this the lack of awareness, low number of referrals for ECMO to these centers and high refusal rate on financial grounds, the learning curve is expected to be fairly prolonged in Indian centers.

Lack of Awareness

The presence of specialized ECMO centers just might not be enough, if the physicians at the referring centers are not aware of the modality. Even if they are aware, knowledge about the criteria, indications, and contraindications of ECMO are of paramount importance. The sole aim being that patients requiring ECMO should receive it at the optimum time, before they are beyond the point of no return, as excessive delay can lead to unwanted outcomes.

Lack of Uniform India-specific Guidelines/Protocols

Whatever protocols and guidelines are available come from western literature^{10,16,17} and centers. Though most hold true for Indian patients, eventually home-grown protocols and guidelines will be needed. Guidelines pertaining technical aspects, flows, and cannula sizes might not hold true for Indian patient's anatomy and physiological needs. Moreover, Indian socioeconomic scenario is widely different from the western guidelines. But considering that ECMO is still evolving in India, national guidelines might still be a bit far off the horizon.

Cost Implications and Constraints

In a country, where 89.21% patients at private hospitals still pay from their pockets (World Bank figures; 2014).²¹ Thus, it is all but natural that an expensive modality like this one will not be easily embraced by the critically ill. Not only that after spending a large amount, a favorable result will be expected impatiently, which can never be guaranteed in a state like this, which has a survival of 54% even in international literature. Moreover, there is always a danger of ECMO stretching out over days and weeks; patients maintaining well on ECMO but not tolerating weaning as the lungs are not yet up to it. The question of withdrawing ECMO will always arise when the family will run out of money or patience. So will this amount to withdrawal of treatment. Will this be contrary to Indian laws? It remains to be answered.

Healthcare Setups

Keeping in mind the limited resources, expertise, and intricacies involved, the most efficient and effective model for development of the modality will be the "Hub and Spoke" model. This has been widely accepted all over the world and running successfully. Extracorporeal membrane oxygenation-referral centers need to be setup with all the expertise, equipment, and support teams all in one tertiary care center with facilities for handling such case including transport rather than having several small ECMO programs running in each and every hospital in a region. The advantages of this model are:

- Efficient accumulation of resources in one place
- Increased case load will lead to a shorter learning curve and better outcomes
- Protocolized care again will improve outcomes.

This concept needs to be coupled with an efficient and capable transport network to decrease the response time and heightened awareness amongst the referring hospitals and physicians to encourage early identification and referral.

Regular CME's, conferences, outreach sessions, awareness campaigns, etc. can be instrumental in achieving this goal. Else it might just become a "salvage therapy" rather a genuine support modality.

***Patient Transport*^{22,23}**

Presently, ECMO is limited to handful of tertiary care centers, whereas the majority of target population is admitted to non-ECMO centers. Understandably, these patients are going to be very unstable and a skilled transport team is required, on the ground or in the air, to transport them to ECMO capable centers. Another option is to have mobile ECMO teams, which initiate ECMO at the referring center and then transport the patient on the machine to an ECMO capable center.

***Infection Control*^{24,25}**

The incidence of hospital-acquired infections is much higher in patients on ECLS as blood circulates through an extracorporeal circuit with many connections and branching. Moreover, the vascular system is breached with large-bore cannulas and any infective invasion becomes a great risk. The primary conditions also contribute to the risk. A tight infection control protocol is very important and should be followed without fail. Staff training is the most important step in this direction. Surveillance at regular intervals and aseptic precautions at all points are necessary. In the authors' experience, all the above steps make a big difference; along with them, moving away from open surgical to percutaneous insertion of cannulas also lead to a significant decline in cannula site and blood stream infection (50% candidemia in surgical vs. 0% in percutaneous) at our center.

Data Sharing

Data sharing has been a bane to the accumulation of literature on ECMO, a problem faced in many other modalities also. No mechanism exists in India for recording the data related to ECMO cases at a national level and analyzing and assimilating it. Whatever, data there is, relates to major individual centers. ELSO gathers data from 11 of the centers as above, but it surely misses out data from nonmember centers. There is a major scope for improvement on this front and is much needed for the advancement of knowledge and awareness of this modality.

CONCLUSION

The literature and indications for ECMO have been increasing steadily over the past few years. Although ECMO is still in its infancy in India, the critical care community is waking up to it and accepting it warmly. New centers are coming up and with more expertise, ECMO is becoming safe, secure, and with minimal complications. There is a need to increase awareness about this lifesaving modality and certified training courses for doctor, nurses, and paramedics are the need of the hour. Setting up ECMO programs on the "Hub and Spoke" model may be the right way to develop the modality further and increase the volume and thus expertise at these

centers. The cost of the modality still remains an impediment to its development in the country but as the number of ECMO runs increases, the cost will decrease hopefully in the years to come.

REFERENCES

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374:1351-63.
2. Bartlett RH. Extracorporeal life support for cardiopulmonary failure. *Curr Probl Surg*. 1990;27:623-705.
3. Bartlett RH. Extracorporeal membrane oxygenation revisited, revisited. *Ann Thorac Surg*. 1992;53:738-9.
4. Ventetuolo CE, Muratore CS. Extracorporeal life support in critically ill adults. *Am J Respir Crit Care Med*. 2014;190:497-508.
5. George Makdisi, I-wen Wang. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis*. 2015;7:E166-76.
6. Bartlett RH, Gazzaniga AB, Fong SW, et al. Extracorporeal membrane oxygenator support for cardiopulmonary failure. Experience in 28 cases. *J Thorac Cardiovasc Surg*. 1977;73:375-86.
7. Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138:720-3.
8. Fanelli V, Vlachou A, Ghannadian S. Acute respiratory distress syndrome: new definition, current and future therapeutic options. *J Thorac Dis*. 2013;5:326-34.
9. Schmidt M, Bailey M, Sheldrake J, et al. Predicting Survival after ECMO for Severe Acute Respiratory Failure: the Respiratory ECMO Survival Prediction (RESP)-Score. *Am J Respir Crit Care Med*. 2014;189:1374-82.
10. Extracorporeal Life Support Organisation. (2013). Adult Respiratory Failure Supplement to the ELSO General Guidelines, Version 1.3. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support. [online] Available from: <https://www.else.org/Portals/0/IGD/Archive/FileManager/929122ae88cusersshyerdocumentselsoguidelinesgeneralallecslversion1.3.pdf>. [Accessed November, 2016].
11. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. *Minerva Anestesiol*. 2010;76:534-40.
12. Aubron C, Cheng AC, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. *Crit Care*. 2013;17:R73.
13. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators; Davies A, Jones D, Bailey M, Beca J, Bellomo R, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*. 2009;302:1888-95.
14. Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: part 2-technical considerations. *J Cardiothorac Vasc Anesth*. 2010;4:164-72.
15. Richard C, Argaud L, Blet A, Boulain T, et al. Extracorporeal life support for patients with acute respiratory distress syndrome: report of a Consensus Conference. *Ann Intensive Care*. 2014;4:15.
16. Extracorporeal Life Support Organisation. (2016). ECLS Registry Ann Arbor. [online] Available from <http://www.else.net.org>. [Accessed November, 2016].
17. Extracorporeal Life Support Organisation. (2014). ELSO Guidelines for ECMO Centres. [online] Available from: <http://www.else.net.org>. [Accessed November, 2016].
18. Aokage T, Palmér K, Ichiba S, et al. Extracorporeal membrane oxygenation for acute respiratory distress syndrome. *J Intens Care*. 2015;3:17.
19. Brazzi L, Lissoni A, Panigada M, et al. Simulation-based training of extracorporeal membrane oxygenation during H1N1 influenza pandemic: the Italian experience. *Simul Healthc*. 2012;7:32-4.
20. Mullany DV, Bull TN, Hunt W, et al. Outcomes of the first 30 cases of an adult extracorporeal membrane oxygenation program: strategies to manage the "learning curve" and implications for intensive care unit risk adjustment models. *Crit Care Resusc*. 2012;14:119-29.
21. World Health Organization. (2014). Out-of-pocket health expenditure. [online] Available from <http://data.worldbank.org/indicator/SH.XPD.OOPC.ZS>. [Accessed November, 2016].
22. Starck CT, Hasenclever P, Falk V, et al. Interhospital transfer of seriously sick ARDS patients using veno-venous extracorporeal membrane oxygenation (ECMO): Concept of an ECMO transport team. *Int J Crit Illn Inj Sci*. 2013;3: 46-50.
23. Lucchini A, De Felippis C, Elli S, et al. Mobile ECMO team for inter-hospital transportation of patients with ARDS: A retrospective case series. *Heart Lung Vessel*. 2014;6:262-73.
24. Sun HY, Ko WJ, Tsia PR, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. *J Thorac Cardiovasc Surg*. 2010; 140:1125-32.
25. Douglass BH, Keenan AL, Purohit DM. Bacterial and fungal infections in neonates undergoing venoarterial extracorporeal membrane oxygenation: an analysis of the registry data of the extracorporeal life support organization. *Artif Organs*. 1996;20:202-8.

Synchrony During Assisted Mechanical Ventilation

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INTRODUCTION

Mechanical ventilation is the most common intervention in intensive care unit (ICU) for a patient with acute respiratory failure. The aim of mechanical ventilation is to reduce work of breathing (WOB), unload respiratory muscles, optimize gas exchange and buy time for the primary pathology to respond to appropriate medical treatment.¹ However, patient ventilator asynchrony (PVA) during mechanical ventilation may cause distress, discomfort, delayed weaning, prolonged ICU stay, and may affect the outcome, adversely.

TYPES OF VENTILATOR ASYNCHRONY

A mechanical breath consists of four phases: (i) triggering, (ii) inspiratory flow phase, (iii) cycling off, and (iv) expiratory phase. There can be asynchrony between patient and ventilator in any of these phases. Among the different types of PVA, the most common is ineffective efforts by the patient which has other synonyms as ineffective triggering, untriggered breaths or trigger asynchrony, in which the patient's inspiratory effort does not trigger the ventilator to initiate the breath.² Commonly, an ineffective effort (during the expiratory period) is defined as an abrupt decrease in airway pressure (usually 0.5 cmH₂O or more) with a simultaneous decrease in expiratory flow, not resulting in an assisted breath from the ventilator.³ However, it can also occur during inspiratory phase where it is seen as a sudden increase in inspiratory flow [during pressure-support ventilation (PSV)] or an instantaneous transient decrease in airway pressure [during volume-controlled continuous mandatory ventilation (VC-CMV)] without triggering an additional breath.² These may be the consequence of dynamic hyperinflation, reduced respiratory drive (including from excessive sedation), respiratory muscle weakness, or an insensitive trigger setting on the ventilator.⁴ Other forms of

trigger asynchrony are double triggering, autotriggering and delayed triggering. Double triggering can be defined as two consecutive inspirations with an interval of less than half of the mean inspiratory time (TI), where the first one is patient triggered. This is known to occur, if the patient ventilatory demand is high, delivered ventilatory support is insufficient or due to mismatch between neural TI and mechanical TI, i.e., TI set on ventilator. In other words, neural TI is longer than the TI set on the ventilator.^{2,3,5} In ideal circumstances, an assisted mechanical breath should be delivered as a consequence of triggering caused by patients inspiratory effort, however, it may occur in absence of any patient trigger, the entity is known as autotrigger. It is reported to occur due to random noise in the circuit, water in the circuit causing abrupt changes in circuit resistance, due to leaks in the circuit and cardiogenic oscillations.^{5,6} Delayed triggering is when the patient triggers a breath and inspiratory gas delivery by ventilator is abnormally delayed, this form of asynchrony has been well taken care of with advent of recent technological advances.²

Flow asynchrony can be found where patient's ventilatory demand is high, but the ventilator is unable to deliver flow as per demand. This can be treated by increasing peak inspiratory flow rate or by changing the mode of ventilation to a pressure-control or variable-flow mode.

Cycling asynchrony occurs due to mismatch between neural (patient) and mechanical (ventilator) TI. When the mechanical TI exceeds the neural TI, the ventilator continues to deliver breath while the patient tries to exhale or the situation opposite to it is when neural TI is greater than mechanical TI, in which case mechanical breath is terminated while the patient continues to be in inspiration. The term for this type of asynchrony is prolonged cycling for the former where the TI is more than double the mean TI and premature cycling for the later, if TI is less than 50% of the mean TI.²

EPIDEMIOLOGY OF PATIENT VENTILATOR ASYNCHRONY AND THEIR CONSEQUENCES

Patient ventilator asynchrony can have a range of manifestation from patient fighting ventilator to imperceptible asynchrony.⁷ The ideal method for detection of PVA is measurement of esophageal pressure by esophageal balloon or measuring electrical activity of diaphragm, however, due to their complexity, these modalities are seldom used in clinical practice and are mostly employed for research purposes. Bedside ventilator waveform analysis provides an acceptable, reproducible, noninvasive, and attractive method of detection of asynchrony.^{1,2} Studies have used asynchrony index (AI) as a method to quantify the PVA events in an individual patient, and most studies have taken an incidence of more than 10% AI as clinically significant and worth treating. Asynchrony index can be calculated by:^{3,8}

$$\text{AI (expressed in \%)} = \frac{\text{Number of asynchrony events}}{\text{Total respiratory rate (ventilator cycles + wasted efforts)}} \times 100$$

A study by Thille et al. done in 62 patients showed that 24% of patients had AI of greater than 10%. In this study, the highest number of PVA events were ineffective triggering with a frequency of 85%, and double triggering comprising of 13%, was the next common event. Other significant observation was that patients who had AI more than 10% required prolonged mechanical ventilation and tracheostomy was common.³ Another prospective cohort study was done by de Wit et al. where they recorded pressure-time and flow-time waveforms for 10 minutes within the first 24 hours of initiation of mechanical ventilation in 60 patients. They calculated ineffective triggering index (ITI) by dividing the number of ineffectively triggered breaths by the total number of breaths. They observed that 16 of 60 patients had ITI greater than or equal to 10%. The study concluded that ITI of greater than or equal to 10% is an independent predictor of longer MV duration (10 days vs. 4, $p = 0.0004$) and shorter ventilator-free survival (14 days vs. 21, $p = 0.03$), however, mortality did not differ between the two groups.⁹ de Wit et al. in another observational study, which included 20 medical ICU patients, did 15 minutes recording of airway pressure and airflow waveform. The highest number of asynchrony events was ineffective efforts, seen in 85% of patients followed by double-triggering, premature cycling and delayed cycling in decreasing order. Ineffective triggering was associated with higher levels of sedation, as assessed with the Richmond Agitation-Sedation Score and the Confusion Assessment Method. The study delineates the fact that though the sedated patients look calm still they have higher events of PVA as compared to alert patients. The deeper level of sedation reduces the respiratory drive, which culminates into weaker muscular effort by patient causing ineffective triggering.¹⁰ Vignaux et al. in a multicenter study observed 60 patients receiving

noninvasive ventilation for acute respiratory failure. Airway pressure, flow, and surface diaphragmatic electromyography were recorded continuously for 30 minutes. Patient ventilator asynchrony events were recorded as double triggering in nine (15%) patients, autotriggering and ineffective breaths were present in eight (13%) patients, premature cycling in seven (12%), and late cycling in 14 (23%) patients. An AI more than 10%, indicating severe asynchrony, was present in 26 patients (43%), whose median (25–75 IQR) AI was 26 (15–54%). A significant correlation was found between the magnitude of leaks and the number of ineffective breaths and severity of delayed cycling.¹¹ Various studies listed above point to different prevalence of PVA in the subset of patients they studied. Hence, it seems difficult to exactly define its prevalence. The reason could be disparity in protocols related to period of observation, day of observation from day of ICU admission, disease state of patient, cause of acute respiratory failure and mode of ventilation. However, some general principles can still be extracted from these studies that even if PVA does not affect mortality still it has a significant effect on morbidity such as increased duration of ventilation, ICU, and hospital length-of-stay.

DETECTING PATIENT VENTILATOR ASYNCHRONY

Clinically, PVA can be assessed by parameters like tachycardia, tachypnea, paroxysmal breathing, and patient's agitation. The preferred method for discerning PVA is by bedside analysis of airway flow and pressure waveforms. The accuracy of this method closely correlates with other methods, viz., measuring of esophageal pressure or electromyography of diaphragm. Due to their invasiveness, these methods cannot be recommended in day-to-day care of the critically ill patients.

Multiple other factors can affect a clinician's ability to detect PVA like training, previous experience, mode of ventilation, and type of patient ventilator interaction.⁷ In a study by Colombo et al. they randomly selected 10 experts and 10 nonexperts (ICU residents and physicians) based on their ICU experience, who were asked to analyze 5 minutes report displaying airflow and airway pressure-time tracing. The instances of asynchrony identified by experts and nonexperts were compared with those ascertained by three independent examiners who evaluated the same reports. The experts had additional information about the tracings of diaphragm electrical activity (EAdi). The study concluded that the ability of ICU physicians to recognize patient-ventilator asynchrony was overall quite low and was further decreased with increase in prevalence; the study also suggested the need for adjunctive measures like esophageal pressure or transdiaphragmatic pressure to facilitate recognition of remaining undetected asynchronies.¹¹ More recently, there has been introduction of objective methods like computerized algorithms in literature to detect PVA.

Chen et al. studied 14 adult mechanically ventilated patients for PVA. The computerized algorithm detected more than 90% of ineffective triggering in expiratory phase.¹² Another objective method has been recently validated in a study of 24 mechanically ventilated adult patients by Sinderby et al. In this study, patient-ventilator interactions were evaluated by comparing ventilator pressure and EAdi waveforms, recorded during pressure support ventilation. The study devised a new index of patient-ventilator interaction (NeuroSync index). In the study, the NeuroSync index appears to be more sensitive in determining patient-ventilator interaction than previous methods.¹³ Another novel approach was devised by Gutierrez et al. in a prospective, observational study of 110 mechanically ventilated adult patients. They did spectral analysis of airway flow and pressure signals. They found that the frequency spectrum of patients who were having synchronous ventilation were characterized by sharply defined peaks spaced at multiples of mean respiratory rate, however, it was less organized in patients with ventilator asynchrony.¹⁴ Due to lack of availability of trained staff who can continuously monitor each and every patient at bedside at all the time, it becomes mandatory to develop automated and objective methods to detect PVA and physician should promptly act to manage it and monitor, if the management is successful or some other cause needs to be handled.

STRATEGIES TO IMPROVE PATIENT-VENTILATOR INTERACTION

Lung inflation occurs to effect gas delivery to the alveoli. For this to occur, sufficient force is needed to overcome the elastic and resistive forces of lung, chest wall and airways.¹⁵ This is largely done by the diaphragm, which by its piston-like action expands the thorax and pushes abdominal contents away. During increased ventilatory demand external intercostals and accessory muscles of inspiration are recruited, which help diaphragm by lifting and expanding the rib cage.¹⁶ Importantly, in the supine position the role of the intercostal muscles are diminished.

These respiratory motions can be easily represented with a simplified equation. If we consider the pressure needed to overcome the total loads of the respiratory system to be P_{tot} , loads offered by elastic recoil as P_{el} and that needed to overcome the airway resistance as P_{res} for a given flow and volume change (ΔV) then:

$$P_{tot} = P_{el} + P_{res}$$

$$P_{tot} = \Delta V / C_{rs} + R \times V$$

Where C_{rs} and R represent respiratory system compliance and airway resistance, respectively.¹⁶ Individual small contributions of inertness and lung tissue resistance are generally disregarded.

Mechanical ventilation is mainly needed when there is increased ventilation need or decreased oxygen (O_2)

supply (hypoperfusion/hypoxia, etc.) or if there is abnormal respiratory system mechanics leading to increased mechanical loads (e.g., increased airway resistance, decreased compliance, etc.). Reasonable duration of ventilator support helps the patients to tide over these periods of crisis.¹⁷⁻²⁰ However, patient-ventilator dyssynchrony can also result in increased loads on ventilatory muscles and hence defeats the purpose of mechanical ventilation.

We need to assess the effective unloading of mechanical loads on ventilator muscles by calculating the single value—work done (W) or the pressure time product (PTP) for the inspiratory muscles. Work is the integral of pressure over change in volume. Pressure time product relies on the pressure changes during respiratory cycle and TI and it correlates better with the ventilator muscle energetics and O_2 consumption than work (W) does and hence is increasingly used clinically to measure the energy demands on ventilator muscles.²¹⁻²³

Pressure time product has led to the concept of PTI (pressure-time index), which can be calculated by the inspiratory pressure (PI) generated, maximum pressure generating capabilities of inspiratory muscle (P_{max}) and TI as the fraction of the ventilator duty cycle (T_{tot}).

$$PTI = (P_i / P_{i_{max}}) \times (T_i / T_{tot})$$

The normal value of PTI for healthy individuals is less than 0.05 (at rest) and goes maximally up to 0.10 during intense exercise. Ventilatory failure occurs, if the value of PTI for diaphragm goes above 0.15 and 0.3 for accessory inspiratory muscles, the highest tolerable value for diaphragm being lesser than for accessory muscles as diaphragm normally operates at submaximal capability even in normal individuals.²¹

Acute respiratory failure sets in, if any of the above components change unfavorably, leading to ventilatory muscle failure (Fig. 1). Thus, while managing a patient with respiratory failure, all these factors should be optimized:

- Minimize loads due to primary disease process
- Minimize loads due to ventilator
- Minimize demands caused by excessive ventilation
- Minimize patient dyspnea/discomfort leading to inappropriate ventilation patterns
- Maximize muscle-metabolic support.

The desired objective to attain harmony between patient's demand and ventilator's delivery may require careful ventilator setting, which assures optimal concurrence of all the phases of breath delivery.

Optimizing Breath Triggering

Triggering asynchrony is of three types:

- Ineffective triggering
- Double triggering
- Autotriggering.

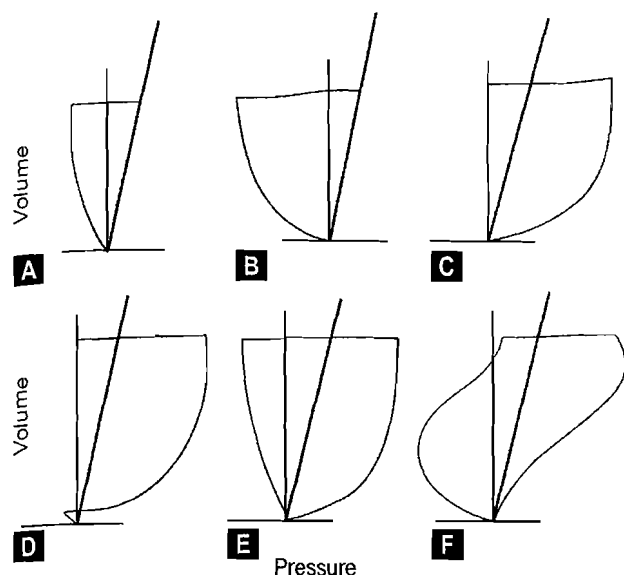
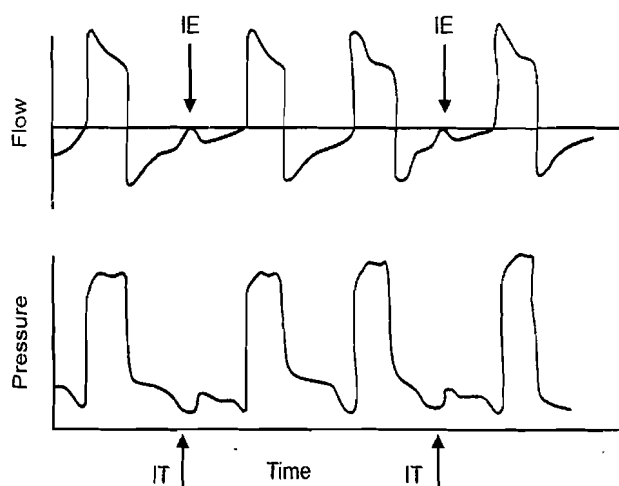


FIG. 1: Various patient-ventilator flow interactions as seen in pressure-volume plots (pressure on the X-axis, volume on the Y-axis). Pressure to the left of the thick diagonal line is patient generated and the work performed by the patient (the shaded area). Area to the right of the thick diagonal line represents ventilator-generated pressure and the work performed by the ventilator is the open area. **A,** It represents the normal work of breathing in a normal patient with no ventilator assistance. **B,** It represents high work of breathing in a patient with respiratory failure, no ventilator assistance. **C,** High work of breathing totally decreased in a patient with respiratory failure while on proper ventilator assistance. **D,** Here, only the work needed for triggering is done by the patient—and rest of the work is done by the ventilator. **E,** Here, the ventilator provides assistance in a way that that the patient's work pattern resembles normal as in **A**. **F,** In contrast, it shows unphysiologic workload on the ventilator muscles because of improper ventilator assistance. While mechanically ventilating a patient, our goal should be optimizing the patient ventilator synchrony to get a pattern as shown in **E** and to essentially avoid the one shown in pattern **F**.



IE, incomplete exhalation; IT, ineffective triggering.

FIG. 2: Ineffective triggering occurring during expiration phase and inspiration phase both as seen in flow and airway-pressure recordings

Ineffective Triggering

Ineffective triggering is the one in which patient's inspiratory efforts are unable to initiate a ventilator cycle and hence is wasted. It is usually detected in flow and airway pressure recordings as an airway pressure drop, which coincides with a flow increase during the expiratory period. It is not followed by a ventilator cycle (Fig. 2) and it can also occur during the inspiratory period. Although ineffective triggering is possible in all modes of ventilation, it is commoner where the levels of assistance are higher because of associated larger tidal volumes (VTs) and a decreased drive.

Ineffective triggering is of two types. The first is missed or delayed triggering due to an insensitive or poorly responsive triggering system. On most ventilators, there are two types of triggering system: (i) pressure trigger and (ii) flow trigger. In pressure trigger, a patient's effort is sensed through a drop in the circuit pressure, while in flow trigger it is sensed by a change in a circuit bias flow.^{5,24} An ideal trigger should be the one (flow or pressure) which is most sensitive and responsive to patient's efforts and thus prevent missed triggering.^{15,16} Both types of effort sensors are incorporated in some ventilators and they respond to the signal (pressure or flow), whichever is detected first. The sensitivity of the triggering system, with either sensor, should be adjusted to be as sensitive as possible, but at the same time, it should not produce autotriggering.^{15,16} Second type of ineffective triggering occurs due to auto or intrinsic positive end expiratory pressure (PEEPi). Here, an inspiratory effort by the patient fails to overcome the work load imposed because of PEEPi and, therefore, fails to trigger a ventilator breath. PEEPi results from incomplete expiration, leading to dynamic hyperinflation, very often present in patients with chronic obstructive pulmonary disease. There are several clinical strategies, which help in preventing trigger dyssynchrony due to PEEPi.

Reducing the PEEPi

By reducing minute ventilation, e.g. reduce set rate, reduce set PI, reduce set VT, minimize causes leading to increased ventilation needs, thus decreasing patient efforts, lengthening the expiratory time (for optimal lung emptying) or improving airway mechanics.²⁵

Application of Extrinsic PEEP

Applying circuit PEEP serves to narrow the gradient between circuit (extrinsic) and PEEPi.^{25,26} This will further reduce the work needed to be done by the inspiratory muscle to trigger the ventilator. Auto-PEEP can be guided by an esophageal pressure monitoring and the resulting trigger dyssynchrony can be managed by providing about 70–80% of measured PEEPi as circuit PEEP.^{27,28} If esophageal pressure monitoring is not available than extrinsic PEEP can be empirically titrated and patient's response is monitored.⁴ In case, the patient is benefiting with the extrinsic PEEP

then there will be: (i) shortening of the delay between patient's effort and ventilatory triggering and (ii) the patient will be more comfortable. At the same time, the ventilator breathing frequency and minute ventilation may actually increase because the efforts, which were previously missed are now being triggered, hence subsequent adjustments are required to avoid excessive ventilation. One important sign to look for is the pressure required for the VT. As long as the applied PEEP is less than the PEEPi, this PI/VT relationship will not change.²⁹ If the applied extrinsic PEEP goes above the PEEPi, end-PI will increase in flow-volume-targeted ventilation or the VT gets reduced in pressure-targeted ventilation.

Double Triggering and Premature Termination of the Breath

Double triggering usually occurs when the patient's ventilator demand is high and TI set on ventilator (ventilator TI) is short. Here, patient's effort (i.e., neural TI) is longer than ventilator TI, so that the patient's effort continues even after the end of ventilator TI, triggering a second ventilator insufflation, as a result there will be a very short or absent expiratory period between two consecutive ventilator cycles.

Double triggering occurs chiefly with assist control ventilation (ACV) when VT is set low with high-flow rates (thus presenting short ventilator TI). Incidence of double triggering is much lesser with PSV (pressure support ventilation), where ventilator TI partly depends on the patient's inspiratory effort. Usually, the TI with PSV tends to be longer than the patient's neural TI, leading to delayed cycling.¹⁵

Double triggering can be reduced by the following maneuver:

- Increase TI
- Increase VT (assist-control mechanical ventilation mode)
- Increase expiratory trigger sensitivity (PSV mode).

Autotriggering

Autotriggering is said to occur when ventilatory cycle is delivered by the ventilator even in the absence of patient's effort. Autotriggering is usually generated by water in circuit, cardiogenic oscillations or leaks in the ventilator circuit. Managing it depends on the cause and can be managed with a careful search for reversible causes (e.g., water in the circuit and small leaks) and/or by adjusting the trigger sensitivity.^{5,24}

Optimizing Flow Asynchrony (Fig. 3)

Commonly used breath types in ICU are flow-targeted volume-cycled breaths and pressure-targeted breaths. Among these flow-targeted volume-cycled breaths are used more commonly as they give the clinician direct control over the flow magnitude, TI, flow delivery pattern and ultimate

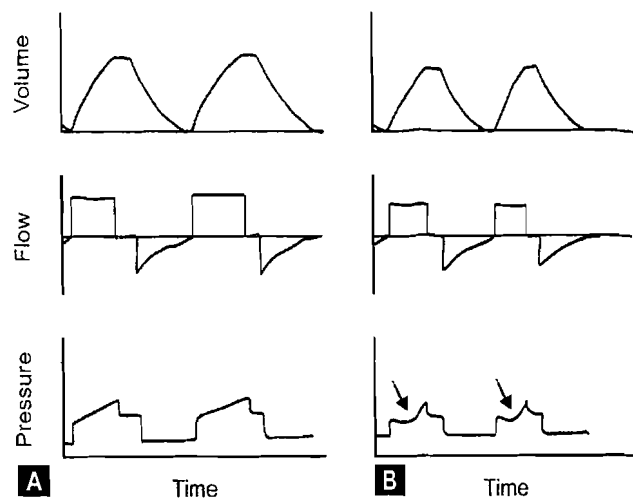


FIG. 3: Graph showing volume, flow and airway pressure over time during six different assisted breaths. **A,** The assisted breath airway pressure profile remains smooth and is not sucked indicating optimal flow and proper muscle unloading. **B,** The right, the airway pressure profile in assisted breath is markedly "sucked down" by patient effort during much of the breath suggesting that the flow delivery is inadequate for patient demand and may lead to inspiratory muscle overload

volume delivered. This can ensure that a safe and effective VT is provided, but, the fixed flow delivery pattern cannot interact with patients ventilatory drive and thus creating flow asynchrony.

Flow-targeted Volume-cycled Breaths

Ventilators have different flow patterns viz., square, sinusoidal, or decelerating. The magnitude and shape of the flow can be adjusted to enhance patient-ventilator synchrony.^{30,31} With proper titration of the flow rates, the synchrony in flow-volume-targeted breaths is almost similar to variable flow, pressure-targeted breaths. This has been well demonstrated by Kallet et al.³² It was also noted in National Institutes of Health acute respiratory distress syndrome network small VT study that with proper attention to flow settings in flow-targeted breaths, sedation requirement did not increase when using small VTs compared with large VTs.³³

Pressure-targeted Breaths

Flow synchrony is much better in pressure-targeted breaths compared to flow-targeted breaths, because of the following advantages with pressure-targeted breaths:

- Flow varies with patient effort and the ventilator delivers whatever flow is needed to attain the set pressure target. This feature enhances flow synchrony, which has been shown in many clinical studies^{32,34} (Fig. 4)
- The time taken to attain the set inspiratory pressure (i.e. pressure rise time) can be adjusted with manipulation of

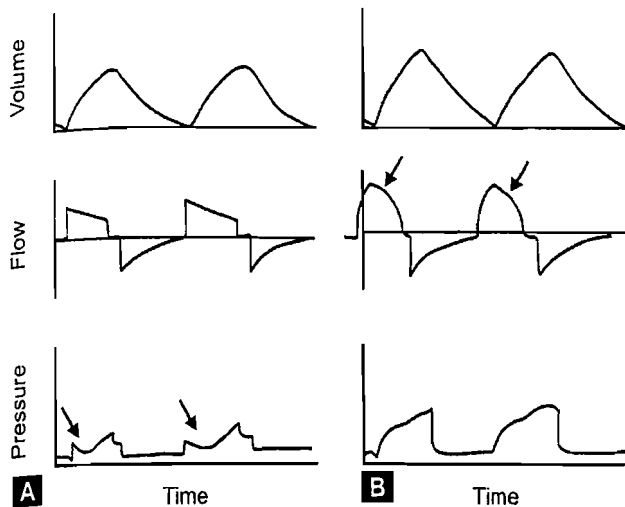


FIG. 4: Enhanced flow synchrony with a variable flow, pressure-targeted breath. The graphs show volume, flow, and airway pressure over time. **A**, A flow-targeted breath where the flow is inadequate and lower than patient's demand and the airway pressure profile is markedly "sucked down" by patient effort (arrow in the airway pressure-time graph) during much of the breath suggesting asynchrony. **B**, A pressure-targeted breath set to deliver a similar tidal volume, the airway pressure profile is smoother and more constantly positive. Here the variable flow (arrow in flow-time graph on right) helps in better synchronization

initial flow delivery, thus decreasing or increasing the rate of rise of PI (also known as flow acceleration adjustment or inspiratory percent or pressure slope).³⁵ In a vigorous effort by the patient, high-flow rates are desirable and it synchronizes better with rapid pressurization pattern, whereas less vigorous efforts may synchronize well with a slower pressurization pattern

- Some ventilators can adjust the circuit pressure profile where it can calculate the resistance offered by the endotracheal tube and compensate for the same. It thus provides a favorable pressure profile in the trachea. No study has yet shown that this feature alters outcome, but observational trials were suggestive of reduced muscle loads.³⁶

A notable concern with pressure-targeted breath is that the control over VT is lost.³⁷ Feedback modes can address this, where the clinician sets a target VT and the ventilator adjusts itself to the pressure required to maintain the set VT. This theoretical appeal is lost when patients efforts changes with pain or anxiety, resulting in inappropriate high VT and leads to inappropriate lowering of the PI.^{38,39}

Optimizing Breath Cycling (Fig. 5)

Optimizing breath cycling involves:

- Delivery of an appropriate VT in accordance with patient demands
- Matching machine's mechanical TI with patient's neural TI.

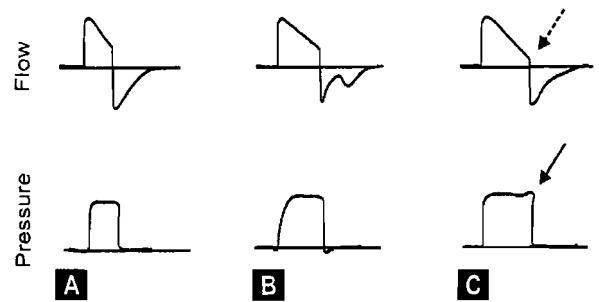


FIG. 5: Examples of cycle dyssynchrony. Figures here show flow and airway pressure over time. **A**, A breath where there is no effort from the patient and machine inspiratory time (TI) is small, which may lead to delivery of an inappropriately small tidal volume. **B**, A shows a breath where ventilator TI is less than patient's neural TI, right—machine TI is less than neural TI, as a result of the persistent effort by the patient the airway pressure profile is pulled downward and there is reversal of expiratory flow after breath termination. It may also lead to double triggering. **C**, A breath where machine TI is greater than neural TI, as a result ventilator lung inflation extends into patient's neural exhalation, consequently the patient activates the expiratory muscles to turn off the breath, which manifest as an elevation in airway pressure at end-inspiration

In flow-targeted volume cycled breaths adjusting these two parameters is quite easy, as VT and TI are independent variables, which can be set or manipulated by the clinicians.

In pressure-targeted breaths, VT and TI depend on the interactions of the following parameters:

- Applied PI
- Respiratory system mechanics
- Patient efforts
- Cycling criteria.

All these parameters are interdependent, as such altering any of these often results in changes in others, making it more difficult to achieve the desired synchrony. In general, higher inspiratory pressure settings, better mechanics, increased effort and longer-cycling criteria settings (e.g., a lower-expiratory flow criterion with PSV and a longer set TI in pressure ACV) extend the machine TI.³⁵ The pressure rise time in PSV can also affect machine TI depending on its effects on the resulting patient ventilator drive and its impact on peak flow and the flow-cycling criteria.³⁵

One common cycling management problem is that, when the patient has a vigorous effort on a pressure-targeted mode, who, despite a low applied PI, still draws VT that may be considered excessive (e.g., >8–10 mL/kg ideal body weight).³³ Here, we have to look for any reversible cause for such high and inappropriate VT, e.g., from pain, anxiety, or central nervous system abnormality. Under these conditions, addressing the inappropriate drive should also be done in addition to ventilator manipulation. If the patient does not have a reversible cause for the excessive inspiratory drive and is not ready for withdrawal of ventilator (e.g., if high PEEP or high fraction of inspired O₂ is needed), many would argue that the high VT should be tolerated and not suppressed with sedation.

NEW MODES OF VENTILATION TO IMPROVE PATIENT VENTILATOR SYNCHRONY

Proportional Assist Ventilation

In proportional assist ventilation (PAV) triggering is as in the conventional modes, i.e., the patient triggers the breath using circuit flow sensor or pressure sensors. Thereafter, the ventilator monitors the flow and volume demanded by the patient and puts a "gain" (set by clinician) on this demand to augment pressure and flow in proportion to the desired reduction of muscle load. Thus, PAV decreases the WOB and improves comfort compared with PSV.⁴⁰ Moreover, Giannouli et al. found that ineffective triggering was much lower with PAV than with PSV because ventilator insufflation time was limited and because VT was smaller at high levels of assistance.⁴¹ Proportional assist ventilation is closer to physiologic ventilation, but knowledge of the resistive and elastic characteristics of the respiratory system is required to set PAV. In awake patients triggering the ventilator, these measurements become unreliable, which in turn leads to an obstacle to its widespread use. However, methods for intermittent automatic determination of respiratory system resistance and elastance have been described recently.^{42,43} Another problem is that there is no minimal pressure or flow provided with PAV, thus it must be used with caution in patients where ventilatory drive is unreliable because of drugs or disease.

Neurally-adjusted Ventilatory Assist

In neurally-adjusted ventilatory assist (NAVA) mode, continuous electromyogram recording of diaphragmatic muscle is done with multiple-array esophageal sensors and the ventilator delivers assistance in proportion to the activity of respiratory muscles of the patient. It provides synchrony with all three phase of breath delivery (trigger, flow, and cycle), at the same time, it can provide patient-driven variability in VT, thus sustaining the advantage of protective lung ventilation. However, like PAV, even here, there is no minimal pressure or flow provided and should be used cautiously when the patient has depressed ventilator drive. Greater efficiency of diaphragm unloading was noted during NAVA compared with PSV with a reduction in the patient's effort and without wasted efforts.⁴⁴ At present, NAVA is a promising but experimental mode of ventilation.

CONCLUSION

Mechanical ventilation is often sought therapy in ICU for patients with acute respiratory failure. Despite the advances in mechanical ventilation, patient ventilator asynchrony is a common occurrence which depends on stage of disease, cause of respiratory failure and mode of mechanical ventilation. PVA adds to morbidity of the patient by increasing

duration of ventilation, ICU, and hospital length-of-stay. Adequate training is required for appropriate diagnosis and characterization of asynchrony. Various objective methods for the same are thus in vogue. Addressing the cause of asynchrony, improves patient comfort by reducing the muscle load and thus positively helps achieving goal of mechanical ventilation. Newer modes of mechanical ventilation offer good physiological rationale however concrete evidence of their supremacy is still lacking.

REFERENCES

- Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med.* 2006;32(1):34-47.
- Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? *Respir Care.* 2011;56(1):25-38.
- Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med.* 2006;32(10):1515-22.
- Racca F, Squadrone V, Ranieri VM. Patient-ventilator interaction during the triggering phase. *Respir Care Clin N Am.* 2005;11(2):225-45.
- Sassoon CSH. Triggering of the ventilator in patient-ventilator interactions. *Respir Care.* 2011;56(1):39-51.
- Kondili E, Prinianakis G, Georgopoulos D. Patient-ventilator interaction. *Br J Anaesth.* 2003;91(1):106-19.
- Murias G, Villagra A, Blanch L. Patient-ventilator dyssynchrony during assisted invasive mechanical ventilation. *Minerva Anestesiol.* 2013;79(4):434-44.
- Pierson DJ. Patient-ventilator interaction. *Respir Care.* 2011;56(2):214-28.
- de Wit M, Miller KB, Green DA, Ostman HE, et al. Ineffective triggering predicts increased duration of mechanical ventilation. *Crit Care Med.* 2009;37(10):2740-5.
- de Wit M, Pedram S, Best AM, et al. Observational study of patient-ventilator asynchrony and relationship to sedation level. *J Crit Care.* 2009;24(1):74-80.
- Colombo D, Cammarota G, Alemani M, et al. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. *Crit Care Med.* 2011;39(11):2452-7.
- Chen CW, Lin WC, Hsu CH, et al. Detecting ineffective triggering in the expiratory phase in mechanically ventilated patients based on airway flow and pressure deflection: feasibility of using a computer algorithm. *Crit Care Med.* 2008;36(2):455-61.
- Sinderby C, Liu S, Colombo D, et al. An automated and standardized neural index to quantify patient-ventilator interaction. *Crit Care.* 2013;17:R239.
- Gutierrez G, Ballarino GJ, Turkan H, et al. Automatic detection of patient-ventilator asynchrony by spectral analysis of airway flow. *Crit Care.* 2011;15(4):R167.
- Marini JJ, Croke PS 3rd. A general mathematical model for respiratory dynamics relevant to the clinical setting. *Am Rev Respir Dis.* 1993;147(1):14-24.
- Polla B, D'Antona G, Bottinelli R, et al. Respiratory muscle fibres: specialisation and plasticity. *Thorax.* 2004;59(9):808-17.
- MacIntyre NR, Leatherman NE. Mechanical loads on the ventilator muscles: a theoretical analysis. *Am Rev Respir Dis.* 1989;139(4):968-73.
- Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl.* 2003;47:3s-14s.
- Gea J, Casadevall C, Pascual S, et al. Respiratory diseases and muscle dysfunction. *Expert Rev Respir Med.* 2012;6(1):75-90.
- Campellone JV. Respiratory muscle weakness in patients with critical illness neuromyopathies: a practical assessment. *Crit Care Med.* 2007;35(9):2205-6.
- Bellemare F, Grassino A. Effect of pressure and timing of contraction on human diaphragm fatigue. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53(5):1190-5.
- Field S, Sanci S, Grassino A. Respiratory muscle oxygen consumption estimated by the diaphragm pressure-time index. *J Appl Physiol Respir Environ Exerc Physiol.* 1984;57(1):44-51.

23. Collett PW, Perry C, Engel LA. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *J Appl Physiol.* 1985;58(4):1263-72.
24. Sassoon CS, Gruer SE. Characteristics of the ventilator pressure- and flow-trigger variables. *Intensive Care Med.* 1995;21(2):159-68.
25. Milic-Emili J. Dynamic pulmonary hyperinflation and intrinsic PEEP: consequences and management in patients with chronic obstructive pulmonary disease. *Recent Prog Med.* 1990;81(11):733-7.
26. MacIntyre NR, McConnell R, Cheng KC. Applied PEEP reduces the inspiratory load of intrinsic PEEP during pressure support. *Chest.* 1997;111(1):188-93.
27. Vitacca M, Bianchi L, Zanotti E, et al. Assessment of physiologic variables and subjective comfort under different levels of pressure support ventilation. *Chest.* 2004;126(3):851-9.
28. Reissmann HK, Ranieri VM, Goldberg P, et al. Continuous positive airway pressure facilitates spontaneous breathing in weaning chronic obstructive pulmonary disease patients by improving breathing pattern and gas exchange. *Intensive Care Med.* 2000;26(12):1764-72.
29. Jubran A, Van de Graaff WB, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1995;152(1):129-36.
30. Come S, Gillespie D, Roberts D, et al. Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. *Am J Respir Crit Care Med.* 1997;156(1):304-8.
31. Manning HL, Molinary EJ, Leiter JC. Effect of inspiratory flow rate on respiratory sensation and pattern of breathing. *Am J Respir Crit Care Med.* 1995;151(3):751-7.
32. Kallet RH, Campbell AR, Alonso JA, et al. The effects of pressure control versus volume control assisted ventilation on patient work of breathing in acute lung injury and acute respiratory distress syndrome. *Respir Care.* 2000;45(9):1085-96.
33. Kahn JM, Andersson L, Karir V, et al. Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. *Crit Care Med.* 2005;33(4):766-71.
34. Chiumello D, Pelosi P, Calvi E, et al. Different modes of assisted ventilation in patients with acute respiratory failure. *Eur Respir J.* 2002;20(4):925-33.
35. MacIntyre NR, Ho LI. Effects of initial flow rate and breath termination criteria on pressure support ventilation. *Chest.* 1991;99(1):134-8.
36. Fabry B, Zappe D, Guttman J, et al. Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilator demand during inspiratory pressure support and automatic tube compensation. *Intensive Care Med.* 1997;23(5):545-52.
37. Kallet RH, Campbell AR, Dicker RA, et al. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. *Respir Care.* 2005;50(12):1623-31.
38. Jaber S, Delay JM, Matecki S, Sebbane M, Eledjam JJ, Brochard L. Volume-guaranteed pressure-support ventilation facing acute changes in ventilatory demand. *Intensive Care Med.* 2005;31(9):1181-8.
39. Jaber S, Sebbane M, Verzilli D, et al. Adaptive support and pressure support ventilation behavior in response to increased ventilatory demand. *Anesthesiology.* 2009;110(3):620-7.
40. Grasso S, Puntillo F, Mascia L, et al. Compensation for increase in respiratory workload during mechanical ventilation. Pressure support versus proportional-assist ventilation. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):819-26.
41. Giannouli E, Webster K, Roberts D, et al. Response of ventilator-dependent patients to different levels of pressure support and proportional assist. *Am J Respir Crit Care Med.* 1999;159(6):1716-25.
42. Younes M, Webster K, Kun J, et al. A method for measuring passive elastance during proportional assist ventilation. *Am J Respir Crit Care Med.* 2001;164(1):50-60.
43. Younes M, Kun J, Masiowski B, et al. A method for noninvasive determination of inspiratory resistance during proportional assist ventilation. *Am J Respir Crit Care Med.* 2001;163(4):829-39.
44. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* 1999;5(12):1433-6.

Section 3

Gastroenterology

SECTION EDITOR: K VINODAN

Care of Post Liver Transplant in Intensive Care Unit

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INTRODUCTION

Orthotopic liver transplantation (OLT) is a treatment option for end-stage liver disease of both acute and chronic etiologies. Improvement in surgical techniques and medical therapy have led to better patient and graft survival rates after OLT with 1 and 5 year patient survival rate of 84% and 67%, respectively.¹ Long-term survivors are at risk for developing various medical complications or liver disease recurrences.

The liver is an organ that actively interacts with all body systems, so that graft recipient faces a myriad of physiological changes. The purpose of this chapter is to focus on the postoperative care of OLT patients and identify potential surgical and medical complications, graft rejection, and common immunosuppressive regimens used post-transplant.

ASSESSMENT OF FUNCTION OF LIVER ALLOGRAFT

A close monitoring of the function of the allograft is required to identify the early and soft signs of graft dysfunction. The recovery of the graft depends mainly on preoperative condition of the recipient, the perioperative stability in terms of hemodynamics, postoperative prevention of graft congestion along with maintenance of sufficient organ blood flow, and donor related factors like quality of graft and surgical aspects.^{2,3}

The assessment of liver allograft can be done using clinical parameters like improving mentation, stable hemodynamics/respiration, serous drain output, or by laboratory tests which could be static or dynamic.

Static tests include monitoring serum bilirubin that gradually normalizes during first week, liver transaminases which may peak during initial 3 days and then slowly settle in case of a normally functioning graft. Synthetic function can be assessed using monitoring hepatic protein synthesis, i.e., serum albumin, coagulation factors (factors V and VII),

or international normalized ratio (INR) levels which should improve without any fresh frozen plasma (FFP) transfusion. Other parameters include decreasing serum lactate, improving platelet counts, and acidemia.

Dynamic tests may include normal flow pattern on Doppler, indocyanine green clearance test.

HEPATIC COMPLICATIONS

Function of liver allograft may be altered by:^{4,5}

- Graft dysfunction
- Rejection
- Technical complications (vascular thrombosis and biliary complications).

Graft Dysfunction

Primary Nonfunction

Primary nonfunction is defined as primary graft failure that results in death or retransplantation within 30 days of primary transplantation.⁶ Its incidence ranges between 2 and 14%.⁶ Exact cause of primary graft failure is not known. Some risk factors include donor factors like advanced age (>50 years), macrovascular steatosis of more than 30% in donor liver, cold ischemia time above 12 hours, and seropositive hepatitis B and C.⁶ Other contributory factors may include severe reperfusion damage and presence of renal failure in recipient. Patient exhibits signs of graft dysfunction like altered mentation, jaundice, raised transaminases (often >5000 U/L), coagulopathy (deranged prothrombin time/activated partial thromboplastin time), hypoglycemia, and oliguria. Management included FFP transfusion every 4–6 hours or as required, dextrose infusion for hypoglycemia. Other therapies, like plasmapheresis, N-acetylcysteine, and prostaglandin E1, have not shown positive results. In case of no recovery within 24–36 hours, consideration should be given for retransplantation to avoid multiorgan failure.⁴

Small for Size Syndrome^{3,4}

It has often been described in patients receiving split or a partial liver graft from a live donor. Patient presents with delayed synthetic function, poor bile production, and cholestasis. Portal hypertension and congestion in a small graft have been implicated for its causation. Supportive care and prevention of infection are important for graft recovery and patient survival.

Graft Rejection**Hyperacute Graft Rejection**

It is rare and complement and antibody mediated (due to preformed antibodies).³

Acute Cellular Rejection⁶

Its incidence is 15–25%. Diagnosis is made through liver biopsy. It has been defined by Banff international consensus as inflammation of the allograft, elicited by a genetic disparity between the donor and recipient, primarily affecting interlobular bile ducts and vascular endothelia, including portal veins and hepatic venules, and occasionally, the hepatic artery and its branches. It is T-cell mediated and divided into two subgroups:

- 1 Early acute cellular rejection: Appears in less than 28 days post transplantation. It does not usually lead to graft loss and can be managed by pulse dose of immunosuppression
- 2 Late acute cellular rejection: Appears in more than 28 days post-transplant and is usually due to under dosage of immunosuppression. It is associated with a worse prognosis and development of graft loss.

Increase in baseline immunosuppression, pulse steroid, use of mycophenolate, or switching to tacrolimus (if patient was on cyclosporine) can be helpful in mild rejection.⁴

Repeated steroid boluses and/or antithymocyte globulin may be given for severe rejection.

Chronic Rejection

It is extremely rare, accounting for less than 5% of all cases of graft loss. It may occur due to noncompliance to immunosuppression, unattended acute rejection, or unknown mechanism. Clinically, it may manifest with cholestatic features and on liver histology as advancing arteriopathy and degenerating bile ducts.

Technical Complications**Vascular Thrombosis**

Hepatic artery thrombosis is the most common (incidence 4–12%)³ and potentially life-threatening vascular compli-

cation. It is seen more commonly in children and in grafts with discrepancy in donor and native vessel size. Causes include poor arterial flow, increased sinusoidal resistance, preservation injury, anastomotic site stenosis, and hypercoagulability. It can present either as hepatic gangrene with sepsis and fulminant liver failure or delayed bile leak from ischemic necrosis of biliary radicals or recurrent bacteremia.⁴ Doppler ultrasonography is a useful method to determine arterial patency. Arteriography may be used for definitive diagnosis where vessel cannot be well-visualized. Management includes revascularization by arterial thrombectomy either by interventional radiology or surgically.^{3,4} If it manifests within 48–72 hours, surgical thrombectomy can be performed. If manifestation is delayed, interventional radiologists can perform intra-arterial catheter thrombolysis.⁷ When revascularization fails, urgent retransplantation is mandatory.

Portal vein thrombosis (PVT) is less common (in <2% of OLT cases)⁸ and present with persistent ascites, intestinal congestion, and bleeding. It occurs because of pretransplant PVT or technical problems. Doppler ultrasonography followed by conventional angiography or magnetic resonance angiography can aid in diagnosis. Management includes thrombectomy either surgically or interventional radiology for graft survival.

Biliary Complications

This is the most common technical complication after liver transplant with incidence ranging from 15 to 20%.⁸ They have been described as “Achilles heel” of liver transplant. These range from early anastomotic leaks, biliary tract ischemia, or technical error to late stricture and obstruction of biliary system. Increasing cholestasis suggested by rising serum bilirubin, alkaline phosphatase, G-glutamyl transferase, and leukocytosis indicates biliary complication. Imaging modalities, like ultrasound, abdominal computed tomography scan, or cholangiography, can help in diagnosis. Treatment options for bile leak include endoscopic retrograde cholangiopancreatography with biliary stenting or percutaneous transhepatic cholangiography with external drainage or surgical repair.

Biliary strictures can be managed using endoscopic or percutaneous balloon dilatation, stenting, or surgical re-exploration.

**CARDIOVASCULAR
SYSTEM CONSIDERATIONS**

Early postoperative phase may be complicated by significant hemodynamic instability. The hyperdynamic, vasodilated preoperative state persists into the early postoperative period and absence of this may indicate volume depletion or myocardial dysfunction.⁹ Intraoperative blood loss and massive fluid shift, preexisting/new left ventricular

dysfunction, hypothermia, acidosis, and electrolyte disturbances can contribute to circulatory dysfunction. Meticulous assessment of fluid status is of paramount importance as relative hypovolemia and fluid overload, both can contribute to graft dysfunction. Fluid administration should be ideally guided by dynamic parameters like stroke volume variation, pulse pressure variation, extravascular lung water, and pulmonary vascular variability index.^{10,11} Use of pulmonary artery catheter is less popular these days. Careful volume expansion with fluid administration and maintenance of mean arterial pressure with vasopressors and inotropes should be done to maintain graft and systemic perfusion. Combination of crystalloid and colloid can be used for volume expansion. Balanced crystalloid contains lesser chloride and prevents hyperchloremic metabolic acidosis. Early administration of albumin may help in reducing the total amount of intravenous fluid while maintaining plasma oncotic pressure. Continuous infusion of 20% albumin is routine at most of the centers in early postoperative period though evidence in this regard is not conclusive.

Hypertensive response is very common in early postoperative period. Postoperative pain, anxiety, volume overload, preexisting hypertension, and administration of drugs, like cyclosporine and tacrolimus, can contribute to it. Blood pressure should be controlled with short-acting agents like labetalol or hydralazine in the early stage and long-acting agents can be introduced later.

Some patients may develop stress cardiomyopathy but it usually reverse spontaneously after a few days to a week.¹² Acute coronary syndrome is relatively uncommon in early postoperative days, however, if it is suspected, decision regarding coronary intervention, antiplatelet, or other supportive care should be taken in consultation with cardiologist and transplant team.

Perioperative arrhythmias may be secondary to hypercapnia, hypoxemia, electrolyte imbalances, metabolic acidosis, myocardial dysfunction, or irritation by central venous catheters. Atrial fibrillation may develop due to perioperative fluid shifts and electrolyte abnormalities.¹³ Treatment with β -blocker and calcium channel blocker is preferred over amiodarone because of its potential hepatotoxicity.

Cardiac tamponade should be considered in the differential diagnosis of low cardiac output with high filling pressure. Superior aspect of Mercedes-Benz incision may violate the pericardial reflection, resulting in pericardial effusion/tamponade. Other medical factors, like renal failure and coagulopathy, may also be contributory.

Patients with portopulmonary hypertension (POPH) may worsen in perioperative period. Exacerbation of POPH and associated right ventricular dysfunction can adversely affect graft function and survival.¹⁴ Preoperative treatment, such as sildenafil, bosentan, and intravenous epoprostenol, should be continued perioperatively. Additionally, inhaled nitric oxide (at doses of up to 80 ppm) can be delivered into the

breathing circuit to reduce pulmonary artery pressures. In refractory cases, placement of a right ventricular assist device or atrial septostomy has been described.

RESPIRATORY SYSTEM CONSIDERATIONS

Most of the patients can be extubated within few hours of surgery, but that depends on institutional practice. Various studies suggest that early extubation is safe and reintubation rate is similar to those who are extubated late.¹⁵ Late extubation increases the risk of ventilator associated pneumonia (VAP) and can increase graft congestion.^{16,17} Nevertheless, many times, it is not possible to extubate early in view of hemodynamic instability, persistent encephalopathy, pulmonary edema, severe hypoxemia, or obesity, and a period of ventilation is required before attempting weaning. Difficult weaning may be because of postoperative atelectasis, VAP, pleural effusion, poor cough reflex or excessive bronchial secretion, and perioperative acute respiratory distress syndrome (ARDS). Noninvasive ventilation can be tried in few patients electively post extubation or as a treatment of extubation failure.

Ventilator associated pneumonia is usually seen in patients requiring prolonged ventilation. Semirecumbent position is advisable during ventilation to prevent VAP. Respiratory sample should ideally be obtained by bronchoalveolar lavage in patients suspected of having VAP. Treatment of VAP is to be done according to established guidelines and local susceptibility pattern.

Acute respiratory distress syndrome in early postoperative period may be attributed to multiple causes like severe reperfusion injury, massive blood transfusion, and postoperative infections. Treatment of ARDS should be based on ARDS Network protocol. Low tidal volume with moderate positive end expiratory pressure (PEEP) should be used while ventilating these patients. Since in ARDS, the lung is poorly compliant and does not transmit all the applied pressure to venous system, high PEEP strategy can be utilized in these patients. Very high PEEP (>10 mmHg) though may be associated with venous stasis, congestion, or graft dysfunction. Experience is limited with other treatment strategies like prone position ventilation, high frequency ventilation, or permissive hypercapnea in post liver transplant patients.

RENAL CONSIDERATIONS

Renal dysfunction after liver transplantation is quite common with actual incidence varying between 5 and 50% depending on the diagnostic criteria used.¹⁸ Etiology is multifactorial and includes preexisting renal dysfunction, perioperative hemodynamic derangement, sepsis, drug induced (tacrolimus, cyclosporine), and graft dysfunction. Intravascular volume assessment should be done and hypovolemia should be corrected. Sepsis should be

aggressively treated with broad spectrum antibiotics and source control. Nephrotoxic medication should be avoided. Small percentage of patients may require renal replacement therapy with substantial morbidity and mortality.

NEUROLOGICAL CONSIDERATION

Neurological dysfunction has been reported in 8.3–47% of all patients receiving liver transplantation.¹⁹ Common disorders include encephalopathy, cerebrovascular accident, and seizures. Encephalopathy can be multifactorial and causes include preexisting hepatic encephalopathy, meningitis, sepsis, cerebral infarction, and spinal cord necrosis amongst other. Seizures can be due to cerebrovascular accidents, metabolic and electrolyte derangements, central nervous system infections, drug induced, or due to previous history of epilepsy.

Posterior reversible leukoencephalopathy syndrome is a serious but reversible neurological dysfunction characterized by occipital or parietal extrapontine demyelination. Calcineurin inhibitors (CNIs) are important cause of this condition among others.

Rarely, osmotic demyelination syndrome is seen in some patients mostly related to rapidity of the sodium correction. This condition is characterized by symmetrical demyelination at the base of pons. Treatment is usually supportive.

METABOLIC AND ELECTROLYTE DYSFUNCTION

Postoperative hyperglycemia is quite common and may be due to diabetes mellitus, stress, CNI, steroids, and exogenous catecholamines. Target blood sugar during perioperative period has been debated extensively, and the general consensus is to maintain it in the range of 140–180 mg/dL. Hyperglycemia may impact graft function and it is imperative to control it with insulin infusion titrated to maintain blood sugar in the desired range. Hypoglycemia is an ominous sign and may indicate allograft dysfunction. It should be aggressively corrected with 25 or 50% bolus dextrose and continuous infusion and titration of insulin infusion rate.

Although relative adrenal insufficiency is common in chronic liver disease patients, exogenous steroids are sufficient to maintain the level during perioperative period.

Intraoperatively, hyperkalemia may be seen due to reperfusion or transfusion of large amount of packed red blood cells (RBCs). Treatment of hyperkalemia is with calcium chloride, dextrose insulin infusion, β_2 agonist, sodium bicarbonate, and potassium binding resins. Refractory hyperkalemia requires hemodialysis.

Other common electrolyte imbalances are hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia, and hypernatremia. Hypocalcemia may be because of chelation of calcium with citrate preservative present in packed RBCs. Phosphorus level should be adequately maintained as

hypophosphatemia may contribute to weaning failure and hemodynamic instability.

GASTROINTESTINAL CONSIDERATIONS

Upper gastrointestinal bleeding is less frequent but may occur due to gastritis and stress ulceration. Recurrence of esophageal and gastric varices may be due to reduced portal flow or complete portal vein thrombosis. Bleeding distal to ligament of Treitz may be from jejunojejunostomy site.

Late bleeding (weeks to months) should prompt an evaluation for infections like Cytomegalovirus, or *Clostridium difficile* enterocolitis.

Mild rise in amylase and lipase can be seen in up to 20% of patients, but clinically significant pancreatitis is seen in less than 5%.²⁰ Most of the times, pancreatitis is mild and patient recovers without complications.

POSTOPERATIVE BLEEDING AND COAGULATION MANAGEMENT

Bleeding in postoperative period may necessitate transfusion and/or surgical exploration. Poor graft function, imperfect hemostasis, slippage of a tie, hypersplenism, hypocalcemia, and dilution may contribute to bleeding. Thrombocytopenia is common and lowest level is usually seen on 3rd or 4th postoperative day. Monitoring of coagulation by thromboelastography becomes necessary in cases of significant and persistent bleeding. Thromboelastography can be useful in differentiating between bleeding secondary to incomplete surgical hemostasis,²¹ platelet dysfunction, and coagulation factor defects. Risk of bleeding must be balanced against the risk of hepatic artery or portal vein thrombosis.

INFECTIOUS COMPLICATIONS

Infections are problematic and most common cause of death. These patients are colonized with multidrug resistant infections due to their previous hospitalization. They receive strong immunosuppression in postoperative period and often develop multidrug resistant infections. Antibiotic prophylaxis is given against enteric Gram negative rods and Gram positive organisms. Common infections are wound site, pneumonia, catheter related blood and urinary tract infections, cholangitis, and *Clostridium difficile* infection.

Common causes of wound site infection are *Staphylococcus aureus*, *Klebsiella*, *E. coli*, *Enterobacter*, *Pseudomonas*, anaerobes, and *Enterococcus*. Pneumonia is mainly caused by Gram negative rods. Treatment of bacterial infections generally involves identification of the infective agent (e.g., cultures and antibiotic sensitivities), source control (e.g., catheter removal and debridement), and antibiotics based on the hospital antimicrobial susceptibility patterns. Common fungal infections include *Candida* and *Aspergillus*. *Candida* can be isolated from many sites.

TABLE 1 Common infections in post-transplant period

Time period after liver transplantation		
1 month	1 st –6 th months	After 6 th month
<ul style="list-style-type: none"> • General risks <ul style="list-style-type: none"> ◦ Surgical procedure ◦ Prolonged hospitalization ◦ Prior colonization ◦ Mechanical ventilation ◦ Indwelling vascular and urinary catheterization • Donor transmitted diseases • Bacterial infections including resistant pathogens <ul style="list-style-type: none"> ◦ Bloodstream infections ◦ Pneumonia ◦ Surgical site infections ◦ Intra-abdominal infections ◦ Abscesses ◦ Urosepsis ◦ <i>Clostridium difficile</i> associated colitis • Herpes simplex virus infection: Herpes labialis or genitalis, with potential for disseminated disease • <i>Candida</i> sp. Infections <ul style="list-style-type: none"> ◦ Fungemia ◦ Abscesses ◦ Urosepsis 	<ul style="list-style-type: none"> • General risks <ul style="list-style-type: none"> ◦ Overimmunosuppression ◦ D+/R-mismatch status for viruses ◦ Allograft rejection ◦ Donor-transmitted diseases Repeated biliary tract manipulations ◦ Retransplantation • Bacterial infections continue to occur in some patients <ul style="list-style-type: none"> ◦ Bloodstream infections ◦ Pneumonia ◦ Abdominal infections ◦ <i>Clostridium difficile</i> associated colitis • Opportunistic pathogens <ul style="list-style-type: none"> ◦ Cytomegalovirus ◦ Epstein-Barr virus ◦ Human herpes virus 6 and 7 ◦ <i>Aspergillus</i> sp. ◦ <i>Pneumocystis jirovecii</i> ◦ <i>Nocardia</i> sp. ◦ <i>Mycobacterium tuberculosis</i> ◦ Endemic mycoses ◦ <i>Toxoplasma gondii</i>, among others 	<ul style="list-style-type: none"> • General risks <ul style="list-style-type: none"> ◦ Variable ◦ High risk patients include those with recurrent rejection and allograft dysfunction that would require intense immunosuppression ◦ Minimal immunosuppression: Usual community ◦ Acquired infections and zoster ◦ Intense immunosuppression due to allograft rejection and dysfunction: Infections occurring during the opportunistic period (see middle column) continue to occur; course of chronic, viral hepatitis may be accelerated

More than two sites colonization should be treated same as systemic candidiasis. Echinocandins (caspofungin, micafungin, anidulafungin) should be used as first choice drug for treatment of candidemia. Alternatively, liposomal amphotericin B can be used.

Fungal prophylaxis prevents superficial and deep fungal infections. It should be given to the patients who underwent prolonged surgery, who have received multiple transfusions, severe preoperative illness, preoperative *Candida* colonization, renal dysfunction, retransplantation, and prolonged intensive care unit (ICU) stay. Fluconazole is used for antifungal prophylaxis at most of the places. Alternatively, liposomal amphotericin B can be used.

Cytomegalovirus infection is common in transplant patient. Patient at highest risk are those who are seronegative and have received organ from a seropositive donor. Patient may be asymptomatic or show involvement of single organ (liver, lung, gastrointestinal tract) to multiorgan involvement. Ganciclovir and valganciclovir are the mainstay of treatment. Foscarnet should be used in case of severe neutropenia or if ganciclovir resistance is suspected. Common infections in post-transplant period are summarized in table 1.

NUTRITIONAL CONSIDERATIONS

Preoperative malnutrition has been associated with an increased risk of postoperative infections, respiratory complications, and a prolonged ICU stay. Factors, such as surgical stress, corticosteroid administration, and preoperative malnutrition, enhance the need for nutritional support postoperatively.⁴ Postoperative ileus generally resolves by the 3rd or 4th postoperative day.⁵ In the absence of any contraindications, progressive oral intake is initiated with liquids and advanced to an unrestricted diet. Nasoenteric feeding can be initiated in the patients who have inadequate oral intake. Enteral nutrition is preferred over parenteral nutrition. Adequate nutrition in postoperative period is associated with lesser incidence of infections. These patients should receive 1.5–2.0 g of protein per kilogram of dry weight during the immediate postoperative period because of the markedly increased protein catabolism leading to increased nitrogen loss during this phase.²² Calories should be given approximately at 120–130% of the calculated basal energy expenditure as the energy requirements are only moderately increased in uncomplicated post liver transplant patients.²³ Close monitoring for any electrolyte disturbances should be done.

IMMUNOSUPPRESSION

The most common protocol for immunosuppression includes triple therapy or a dual regimen.² Triple therapy consists of a CNI, antimetabolite agent, and a steroid. Combination of steroids and a CNI constitute dual regimen and has shown to be equally efficacious as triple therapy.

Calcineurin inhibitors include tacrolimus, and cyclosporine.²⁴ They act by inhibition of calcineurin which results in decreased interleukin (IL)-2 production and dampening of T-cell recruitment and activation. Both seem to be similar with regards to graft and patient survival. However, tacrolimus has been associated with lower incidence of acute and steroid resistant rejection. It is most commonly used drug, started within 24 hours post-transplant and dose adjusted as per the trough level. Both are equally nephrotoxic, but tacrolimus is associated with higher chances of diabetes and neurotoxicity and less chances of hypertension and hyperlipidemia. Antimetabolites include mycophenolate mofetil and azathioprine.²⁴ Mycophenolate mofetil is more commonly used, started within 1st week post-transplant. It selectively inhibits purine synthesis, thus inhibiting T- and B-cells proliferation.¹ Mandatory drug monitoring is not required as it is renal sparing.

Glucocorticoids, methylprednisolone intravenous, later changed to enteral is mainly used as part of maintenance protocol.²⁴

Induction therapy with interleukin-2 receptor antibody preparation, that is daclizumab and basiliximab, may be an effective approach.¹ Sirolimus, which is a macrocyclic triene antibiotic, acts by preventing T-cell proliferation and inducing cell cycle arrest.^{1,24} It is increasingly being used for primary and rescue immunosuppression.

CONCLUSION

Liver transplantation has now become an acceptable means for treating end-stage liver disease or fulminant hepatic failure, with excellent long-term outcomes. It has been possible because of multidisciplinary teamwork among transplantation center teams, continued improvements in surgical technique, and post-transplantation immunosuppression regimens. Early recognition, diagnosis, and treatment of postoperative complications have helped in shorter ICU stay and better outcomes.

REFERENCES

1. Futagawa Y, Terasaki PI, Waki K, et al. No improvement in long-term liver transplant graft survival in the last decade: an analysis of the UNOS data. *Am J Transplant*. 2006;6:1398-406.
2. Gopal PB, Kapoor D, Raya R, et al. Critical care issues in adult liver transplantation. *Indian J Crit Care Med*. 2009;13:113-9.
3. Srinivasan S, Govil D. Critical care aspects in adult liver transplantation. Critical Care. 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2016. pp. 253-60.
4. Feltracco P, Barbieri S, Galligioni H, et al. Intensive care management of liver transplanted patients. *World J Hepatol*. 2011;3(3):61-71.
5. Pinsky MR, Grenvik A, Gordon RD, et al. Intensive care of liver transplant patients; 1-49. d-scholarship.pitt.edu/4164/1/31735062129311.
6. Chakravarty D. Early complications of liver transplantation. *Liver Transplantation*. 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2010. pp. 213-74.
7. Srinivasan S, Govil D, KN J. Liver transplant patient. Text book of Critical Care including Trauma and Emergency Care. 1st ed. New Delhi: Jaypee Brothers Medical Publishers; 2016. pp. 642-50.
8. Eghtesad B, Miller CM, Fung JJ. Post-liver transplantation management. *Current clinical medicine/Cleveland Clinic*. 2nd ed. 2010(5):564-71.
9. Nasraway SA, Klein RD, Spanier TB, et al. Hemodynamic correlates of outcome in patients undergoing orthotopic liver transplantation. Evidence for early postoperative myocardial depression. *Chest*. 1995;107:218-24.
10. Reuter DA, Felbinger TW, Moerstedt K, et al. Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2002;16:191-5.
11. Reuter DA, Felbinger TW, Schmidt C, et al. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med*. 2002;28:392-8.
12. Sampathkumar P, Lerman A, Kim BY, et al. Post-liver transplantation myocardial dysfunction. *Liver Transpl Surg*. 1998;4:399-403.
13. Xia VW, Worapot A, Huang S, et al. Postoperative atrial fibrillation in liver transplantation. *Am J Transplant*. 2015;15:687-94.
14. Cartin-Ceba R, Krowka MJ. Portopulmonary hypertension. *Clin Liver Dis*. 2014;18:421-38.
15. Mandell MS, Lezotte D, Kam I, et al. Reduced use of intensive care after liver transplantation: influence of early extubation. *Liver Transpl*. 2002;8:676-81.
16. Chastre J. Conference summary: ventilator-associated pneumonia. *Respir Care*. 2005;50:975-83.
17. Jullien T, Valtier B, Hongnat JM, et al. Incidence of tricuspid regurgitation and vena caval backward flow in mechanically ventilated patients. A color Doppler and contrast echocardiographic study. *Chest*. 1995;107:488-93.
18. Paramesh AS, Roayaie S, Doan Y, et al. Post-liver transplant acute renal failure: factors predicting development of end-stage renal disease. *Clin Transplant*. 2004;18:94-9.
19. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. *Neurology*. 2003;61:1174-8.
20. Krokos NV, Karvias D, Tzakis M, et al. Acute pancreatitis after liver transplantation: Incidence and contributing factors. *Transplant Int*. 1995;8:1-7.
21. Wang SC, Shieh JF, Chang KY, et al. Thromboelastography-guided transfusion decreases intraoperative blood transfusion orthotopic liver transplantation: randomized clinical trial. *Transplant Proc*. 2010;42:2590-3.
22. Chakravarty D. Immunosuppression drugs. *Liver transplantation*. 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2016. pp. 166-80.
23. Shanbhogue RL, Bistran BR, Jenkins RL, et al. Increased protein catabolism without hypermetabolism after human orthotopic liver transplantation. *Surgery*. 1987;101:146-9.
24. Hasse J. Liver transplantation: The benefits of nutrition therapy in the liver transplant patient. In: Klintmalm G (Ed). *Recent Developments in Transplantation Medicine*. Vol. 3. Liver Transplantation. Glenview: Physicians and Scientists Publishing Co; 1996. pp. 81-100.

Challenges in Identifying Sepsis in Liver Failure

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INTRODUCTION

Patients with cirrhosis are highly predisposed for bacterial infections and sepsis leading to rapid decompensation and progression of liver failure. Though there have been significant advancements in molecular diagnostics and biomarkers in the diagnosis of sepsis, the outcomes of patients with sepsis in cirrhotics or acute-on-chronic liver failure remains poor as compared with the general population. This is because early diagnosis of bacterial infections and identification of sepsis in this category of patients is faced with many challenges.

In this review, the authors address these challenges and find out ways to manage these patients in the early stages of sepsis thereby improving the outcome.

EPIDEMIOLOGY

Sepsis is present in 30% of patients with cirrhosis, on admission or during in hospital stay, becoming the major cause of death.¹ In hospital mortality of cirrhotics, who develop septic shock is higher and may exceed 70%.²

The most common infection in cirrhotics and their incidence is depicted in box 1. Sixty percent of bacterial infections in cirrhosis are community acquired and 40% are nosocomial.¹ In the community acquired infections, the causative organisms are Gram-negative bacteria especially *Escherichia coli* (60%), Gram-positive cocci (30–35%), and mixed (5–10%). The pattern is different in nosocomial

infections with 60% for Gram-positive cocci and 30–35% for Gram-negative bacilli as a result of use of therapeutic procedures and previous antibiotic therapies.² Risk factors of infection by Gram-positive bacteria are recent or current hospitalization, receiving quinolones, prophylaxis, and invasive procedures.

There has been a rise in bacterial infections due to multidrug-resistant organisms probably because of the inadvertent use of antibiotics. In a large study, the main resistant organism was extended-spectrum β -lactamase-producing *Enterobacteriaceae*, followed by *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and *Enterococcus faecium*.³

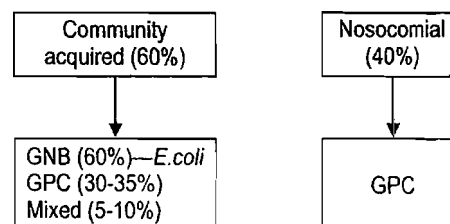
Fungal infections (*Candida* spp.) are present in 15% of severe sepsis in cirrhosis² (Flowchart 1). Clinical risk factors associated with occurrence of bacterial infections in cirrhosis are:^{3–5}

- High child-pugh score model for end stage liver disease >15
- Variceal bleeding—bacterial infections occur in >45% of patients admitted with gastrointestinal bleeding
- Low-ascetic protein levels
- Low-serum albumin
- Prior episode of spontaneous bacterial peritonitis (SBP).

Box 1: Infection and incidence in cirrhotic patient

Types of infection in cirrhotic patient

- Subacute bacterial peritonitis: 25–31%
- Urinary tract infection: 20–25%
- Pneumonia: (15–21%)
- Bacteremia: 12%
- Skin and soft tissue infection: 11%



Fungal infections 15% of cirrhotic patients severe sepsis

GNB, Gram-negative bacilli; GPC, Gram-positive cocci; *E. coli*, *Escherichia coli*.

FLOWCHART 1: Organisms in cirrhotic patients and their incidence

PATHOGENESIS OF SEPSIS IN CIRRHOSIS⁶

Cirrhosis is associated with coexistence of state of immunodeficiency and systemic inflammation and is referred to as cirrhosis-associated immune dysfunction, which increases the susceptibility to infections.

- The state of immunodeficiency occurs secondary to:
 - Loss of immune surveillance function of liver because of damage to reticuloendothelial system of liver (portosystemic shunting and Kupffer cell damage) and reduced synthesis of important proteins involved in innate immunity like complement factors
 - Compromise of the functions of circulating and intestinal populations of immune cells leading to dysfunction of neutrophils, monocytes, B and T lymphocytes, NK lymphocytes.
- Systemic inflammation is secondary to pathologically increased bacterial translocation causing entry of viable intestinal bacteria from intestinal lumen to internal milieu via mesenteric lymph nodes and portal vein leading to "cytokine storm". This is associated with very high levels of proinflammatory markers like tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) from activation of circulating immune cells contributing to sepsis-related organ failures. This proinflammatory phase may be followed by prolonged period of compensatory anti-inflammatory response syndrome, which causes recurrent nosocomial infections and death.

DIAGNOSIS OF BACTERIAL INFECTIONS

Patients with cirrhosis have increased susceptibility to infections due to various reasons explained above and are the major cause for decompensation secondary to sepsis and septic shock accounting for increased mortality rate in this group of patients.

A high index of suspicion is recommended to enable early diagnosis of bacterial infection because many of the signs and symptoms are masked in cirrhosis.

Challenges in Identifying Sepsis in Cirrhotic Patients

- Most of the cirrhotic patients with underlying infection or sepsis present with nonspecific symptoms like lethargy, decreased appetite, somnolence or may even be asymptomatic initially which cause delayed diagnosis¹
- Though systemic inflammatory response syndrome (SIRS) has fallen out of favor after the arrival of updated definition and criteria for sepsis and septic shock (SEPSIS-3),⁷ the criteria are still useful in helping to form a provisional diagnosis of infection in the general population. However, in patients with cirrhosis the SIRS criteria have limited utility.¹

- Temperature response is blunted because of the immunocompromised state
- Total leukocyte counts are usually on the lower side because of hypersplenism
- Most of these patients have baseline tachycardia because of hyperdynamic circulatory state even in the absence of underlying infection
- Patients receiving β -blockers for prevention of variceal hemorrhage have reduced heart rate
- Respiratory rate is usually on the higher side secondary to hyperventilation because of hepatic encephalopathy.

Systemic inflammatory response syndrome is present in 10–30% of decompensated cirrhotic patients without underlying infection. So, it is not the best marker of infection in cirrhosis. However, its presence in patients with decompensated cirrhosis is associated with poor prognosis.

- The utility of updated definition and clinical criteria of SEPSIS [SEPSIS-3—suspected or documented infection and an acute increase by two or more Sepsis Related Organ Failure Assessment (SOFA) points from baseline] in cirrhosis needs to be validated in further studies. The qSOFA (quick SOFA) a screening tool to identify adult patients with suspected infection, who are likely to have poor outcomes incorporating simple bedside criteria—altered mentation, systolic blood pressure of 100 mmHg or less, and respiratory rate of 22 per minutes or greater has limited utility in cirrhosis for the same reasons as mentioned above for SIRS⁷
- Another challenge in the diagnosis of sepsis in decompensated cirrhosis is that the traditional culture method is time consuming and positivity is only 30–70%.¹

Suggested Workup in Diagnosing Bacterial Infections and Sepsis in Cirrhosis

Since a delay in diagnosing infections in cirrhosis can lead to increased mortality identifying infection at the earliest is the biggest challenge. A systematic approach will facilitate and accelerate the diagnosis of underlying infection and sepsis:

Step 1: When to Suspect Infection or Sepsis in Cirrhosis?⁵

Bacterial infection should be suspected in any patient of cirrhosis who gets admitted with:

- New onset or worsening hepatic (portosystemic) encephalopathy
- Worsening of organ dysfunction—renal or hepatic
- Leukocytosis
- Nonspecific signs and symptoms serious enough to warrant admission.

Step 2: General and Physical Examination¹

All patients of decompensated cirrhosis should undergo detailed general and physical examination to identify source of infection which includes:

- Vitals: Core temperature, mentation, blood pressure, pulse, respiratory rate in order to identify symptoms and signs of SIRS, sepsis and septic shock
- Systemic examination:
 - Per abdominal examination—distention, tenderness, bowel sounds (SBP/secondary peritonitis)
 - Respiratory signs (pneumonia and empyema)
 - Any skin related focus of infection such as cellulitis
 - Meningeal signs in association with altered sensorium to rule out meningitis.

Step 3: Investigations^{1,5}

Following tests are to be in patients in whom bacterial infection is suspected:

- Chest X-ray
- Blood culture and urine culture
- Paracentesis is recommended in all hospitalized cirrhotic patients with ascites at the time of admission and/or in case of gastrointestinal bleeding.
 - Ascitic fluid should be sent for neutrophil count and culture (10 mL in a blood culture bottle at bedside)
- Culture and Gram staining of sputum in the presence of symptoms or positive chest X-ray
- Wound culture and cerebrospinal fluid culture when indicated
- Abdominal ultrasonography in case of abdominal symptoms or when the source of infection is not clear and to guide paracentesis in patients with minimal ascites
- If fungal infection is suspected, and in all patients on steroids or immunosuppressive drugs, galactomannan in sputum or bronchoalveolar lavage and cryptococcal serum antigen should be assayed and chest high-resolution computed tomography should be considered.

Step 4: Evaluation of Organ Dysfunction¹

This is important for determining the severity of infection in the form of sepsis and septic shock:

- Cardiovascular system: Mean arterial pressure and blood lactate levels
- Renal: Urine output, mL/day, serum creatinine, mg/dL, venous blood gases
- Hepatic: Serum bilirubin, ascites, and encephalopathy
- Brain: Mental status
- Coagulation: Platelet count, activated partial thromboplastin time, prothrombin time, fibrinogen levels
- Metabolism: Serum glucose levels.

Step 5: Potential Tools for Early Detection of Bacterial Infections**Role of Acute Phase Protein Biomarkers^{1,3,8,9}**

C-reactive protein (CRP) and procalcitonin (PCT) are two potential tools for early detection of the presence and the severity of bacterial infections.

- C-reactive protein: It is an acute phase protein mainly synthesized by hepatocytes and its level in blood is found to increase in response to inflammation or infection. As a systemic marker of inflammation, CRP has high sensitivity but low specificity. In patients with cirrhosis, basal CRP levels are found to be higher than in the general population due to chronic inflammation. During bacterial infection, the rate of rise in CRP levels is lower in patients with advanced liver disease. So, in patients admitted in intensive care unit for decompensated cirrhosis even moderate increase in CRP levels should prompt the intensivist to start appropriate empirical antibiotic
 - C-reactive protein levels can also be utilized as a marker for predicting short-term mortality risk⁹
 - The falling trend in CRP levels during serial measurements can be considered as a marker of resolution of systemic inflammation.

Procalcitonin

It has been well validated and accepted as a marker of infection in the noncirrhotics because of its favorable kinetic property-exhibiting rapid plasma levels (at around 6 hours) after endotoxemia thus helping in the early diagnosis of bacterial infections.⁹ Procalcitonin is produced by nearly all tissues in response to endotoxin or mediators released in response to bacterial infections IL-1b, TNF- α , and IL-6.³

Though there have been conflicting results with regards to its diagnostic accuracy in cirrhotics, the utility of PCT in diagnosing bacterial infection is still good based on studies. Procalcitonin may be helpful to distinguish bacterial infections from viral infection or other noninfectious causes. Further research is indicated to decide about the cut off values.

In a study by Cesar Lazzarotto et al.,⁹ CRP levels >29.5 ng/dL exhibited sensitivity of 82% and specificity of 81% for the diagnosis of bacterial infection in cirrhosis patients.⁹

In a meta-analysis by Lin et al., the authors suggested that the PCT test can be used as a rule-in diagnostic tool (positive likelihood ratio 7.38), CRP test can be used as a rule-out diagnostic tool (negative likelihood ratio 0.23) in patients without signs of infection.¹⁰ The combination of CRP and PCT may slightly improve the diagnostic accuracy of bacterial infection.³

C-reactive protein and PCT levels are reliable markers of bacterial infection in decompensated cirrhosis and predict short-term mortality risk⁹

Potential Tools for an Early Identification of the Pathogen and of Its Susceptibility to Antibiotics⁸

- Real time polymerase chain reaction assays have got potential utility in identifying pathogens early (in <6 hours) as compared to standard culture techniques. This will definitely be useful in diagnosing culture-negative bacterial infections.
 - Limitations:
 - Expensive
 - Time consuming
 - Need special equipment and technical expertise
- Application of Direct Susceptibility Test based on Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) from blood positive blood cultures has been proposed for early detection of resistant bacteria and their antibiotic susceptibility
 - Limitation:
 - Results need to be confirmed by conventional cultures
 - Lack of reliability in mixed infections.

CONCLUSION

Cirrhosis is the most common acquired immunocompromised state and hence predisposes these patients to infectious complications, which is associated with increased mortality rates if not treated in time. Early diagnosis of bacterial infection is crucial in the management of patients

with decompensated cirrhosis. Since the symptoms and signs are subtle and nonspecific in many patients and most of the patients with cirrhosis have baseline SIRS, diagnosis of sepsis requires a high index of clinical suspicion and step-by-step diagnostic approach. Development of rapid and accurate diagnostic tools is urgently required.

REFERENCES

1. Fernández J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol.* 2012;56:S1-12.
2. Gustot T, Durand F, Lebre C, et al. Severe sepsis in cirrhosis. *Hepatology.* 2009;50:2022-33.
3. Bunchorntavakul C, Chamroonkul N, Chavalitthamrong D. Bacterial infections in cirrhosis: A critical review and practical guidance. *World J Hepatol.* 2016; 8:307-21.
4. Bran OS. Infectious complications in cirrhosis. *Curr Gastroenterol Rep.* 2001;3: 285-92.
5. Fagiollet S, Colli A, Bruno R, et al. Management of infections in cirrhotic patients: Report of a Consensus Conference. *Dig Liver Dis.* 2014;46:204-12.
6. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol.* 2014;61:1385-96.
7. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315:801-10.
8. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: A position statement based on the EASL special conference. *J Hepatol.* 2014;60:1310-24.
9. Lazzarotto C, Ronsoni MF, Fayad L, et al. Acute phase proteins for the diagnosis of bacterial infection and prediction of mortality in acute complications of cirrhosis. *Ann Hepatol.* 2013;12:431-43.
10. Lin KH, Wang FL, Wu MS, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis. *Diagn Microbiol Infect Dis.* 2014;80:72-8.

Coagulopathy in Liver Disease

Sumit Ray, Arijit Samanta

INTRODUCTION

Liver is a vital organ in all vertebrate animals. Maintaining homeostasis between the procoagulant and anticoagulant function is one of the many important functions of the liver. Liver synthesizes many hemostatic proteins and thus plays a pivotal role in blood coagulation. Insights into the coagulopathy of liver disease are important for discernible hemostatic management of these patients. This chapter provides an overview of the pathophysiology, clinical, and laboratory features as well as management of bleeding and thrombosis.

PATHOPHYSIOLOGY

Liver produces both procoagulant and anticoagulant factors, thus in liver disease both acute and chronic, there is decreased production of these proteins. As this decline is not equally proportionate, these patients may manifest either with bleeding or with thrombosis. There is also alteration in platelet count, platelet function, fibrinolytic pathway, and functions of von Willebrand factor (vWF). All of these contribute to coagulation abnormality. Thus the historical view of "autoanticoagulated" state is imprecise.

DEFECTS IN COAGULATION FACTORS

Almost all the coagulation factors are produced in liver. Factor VIII and XIIIa are notable exceptions. Though partially, factor VIII is produced in the liver endothelium but majority of factor VIII and XIIIa are produced from bone marrow. Most of the procoagulants are synthesized in the hepatocytes itself, but a few are also synthesized from sinusoidal endothelium or stellate cells. Post-translational modification like glycosylation and gamma carboxylation of some factors (II, VII, IX, and X) also take place in hepatocytes. Anticoagulant proteins like protein C, S and antithrombin are also synthesized in hepatocytes. In liver disease, procoagulant

factor VIII and vWF levels are actually increased.¹ As the vWF stabilizes factor VIII, in liver disease increased level of the vWF also contributes to raised levels of factor VIII. Liver disease with history of alcohol intake complicates the scenario further as alcohol intake causes vitamin K deficiency, which is important for post-translational modification. Dysfibrinogenemia also contributes to the bleeding risks. This erratic and unpredictable dysregulation of both the pro- and anticoagulant proteins leads to a state known as "rebalanced hemostasis".

Platelet

Platelets help in primary hemostasis. In liver disease, platelet dysfunction occurs either quantitatively or qualitatively or both. The reasons are multifactorial. Mild thrombocytopenia (100,000–150,000/ μ L) is seen in 75% of chronic liver disease (CLD) patients and moderate (50,000–100,000/ μ L) in 13% of cases.² Splenomegaly is a well-known complication of CLD due to elevated portal pressure. Platelets may be sequestered in the spleen causing platelet destruction. Due to CLD, thrombopoietin production is decreased leading to reduced platelet production in the bone marrow. Parenteral thrombopoietin is seen to increase the platelet count but at the cost of increased risk of thrombosis, so it is deferred as a therapeutic agent. Further hepatitis C virus (HCV) infection, alcohol, and other infections associated with CLD, antiviral or antibiotic therapy can suppress the bone marrow and lead to thrombocytopenia. Patients with advanced stage of liver disease may also have decreased platelet functions due to association of other complications like uremia, infection, or endothelial abnormalities. Infection is associated with CLD in nearly 30% of cases.³ Infection or endotoxemia may alter the nitric oxide (NO) metabolism and endothelial damage that leads to platelet dysfunction and formation of some glycosaminoglycans known as heparinoids that also have anticoagulant activity.

von Willibrand Factor

von Willibrand factor is also a primary hemostatic agent like platelets and helps in coagulation by helping platelets to adhere. It is synthesized from the endothelium along with factor VIII. In liver disease, the synthesis of vWF is increased.⁴ vWF is cleaved by ADAMTS13, a protein that is produced in hepatocytes. Clearly, in liver disease its production is decreased leading to an increased longevity of vWF. Thus, in primary hemostatic mechanism thrombocytopenia is counterbalanced by increased vWF in liver disease.

Fibrinolysis

The final step in clot formation is the conversion of fibrinogen to fibrin strands by thrombin. Fibrin then cross-links with platelet and forms a clot. This is further stabilized by factor XIII. This clot formation is a dynamic process. That means, it is simultaneously associated with clot dissolution by fibrinolysis and this maintains homeostasis. This homeostasis is disrupted in liver disease leading to a state of hyperfibrinolysis. Evidence of systemic fibrinolysis is seen in 30–46% of cases in laboratory investigations, but clinically significant fibrinolysis is only found in 5–10% of cases of decompensated cirrhosis. Not only does hyperfibrinolysis cause premature clot dissolution, but it also causes consumption of the coagulation factors resembling disseminated intravascular coagulation (DIC), and is known as accelerated intravascular coagulation and fibrinolysis (AICF). Coagulation factors and products of fibrinolysis are normally cleared by hepatocytes and Kupffer cells but in liver disease this function is also jeopardized. This state of hyperfibrinolysis is contributed by several factors:

- Increased level of tissue plasminogen activator that generates plasmin
- Reduced levels of α -2 antiplasmin, factor XIII, and thrombin-activatable fibrinolysis inhibitor
- Elevated levels of fibrin degradation product, like D-dimer due to fibrinolysis that further interferes with the normal coagulation process
- Ascitic fluid, which develops in CLD due to portal hypertension, seems to have fibrinolytic activity. When this fluid is delivered to the systemic circulation through the thoracic duct, it further causes systemic fibrinolysis.⁵

Surprisingly, tests that directly measure clot lysis do not demonstrate this hyperfibrinolytic state in cirrhotic patients so it is mostly underdiagnosed. Though, some studies show hypofibrinolysis during acute liver failure (ALF).⁶

Prothrombotic Changes

Endogenous anticoagulants like protein C, protein S, antithrombin III, and fibrinolytic factors are all produced in hepatocytes. As discussed earlier, hepatocytes also produce ADAMTS13, an important protein that cleaves vWF. As all

these proteins are depleted in liver disease, it produces a state of hypercoagulation. Furthermore, the venous stasis in the portal vein or in the lower limbs due to peripheral edema and endothelial injury as described before, also contribute to activation of other two limbs of Virchow's triad (endothelial injury, stasis, and hypercoagulability), causing increased risk of thrombosis. Unfortunately conventional laboratory tests of coagulation do not reveal this state and it can only be appreciated clinically.

Significance of Types of Liver Disease

The hemostatic abnormalities described earlier are not seen in equal severity in all types of liver disease. They also differ as follows:

- Cholestatic liver diseases like primary biliary cirrhosis and primary sclerosing cholangitis have little effect on antihemostatic mechanisms and may cause portal venous thrombosis. The mild hemostatic abnormality is due to functional change in platelets
- Higher risk of prothrombotic state is associated with nonalcoholic fatty liver disease
- Acute liver failure has a unique characteristic. As the liver failure evolves rapidly in ALF, thrombocytopenia is not a usual feature. On the contrary, deficiency of both pro- and anticoagulants are more marked as compared to CLD.

Diagnostic Approach to Coagulopathy in Liver Disease

Due to the complex interactions between the various portions of the hemostatic arms, different arrays of conventional laboratory investigations do not definitely assess the coagulation status in a patient with liver disease. Frequently measured coagulation parameters like prothrombin time (PT) and activated partial thromboplastin time (APTT) reveal a coagulant-deficient state by showing raised levels, but that does not mean an increased tendency of bleeding episodes as these parameters do not reveal the state of procoagulant activity conferred by protein C, protein S, and antithrombin III. Thus relying only on these traditional tests may cause an inappropriate use of blood products.

For a better and more comprehensive understanding of the hemostatic state of a patient with liver disease, thrombin generation assay is used in research laboratories. One such test uses recombinant tissue factor to assess the effective thrombin generation time in a state when both the anti- and procoagulants remain activated. Unfortunately, these tests have not gained popularity in the clinical setting as they are ineffectual in differentiating between patients with chances of bleeding or thrombosis.⁶

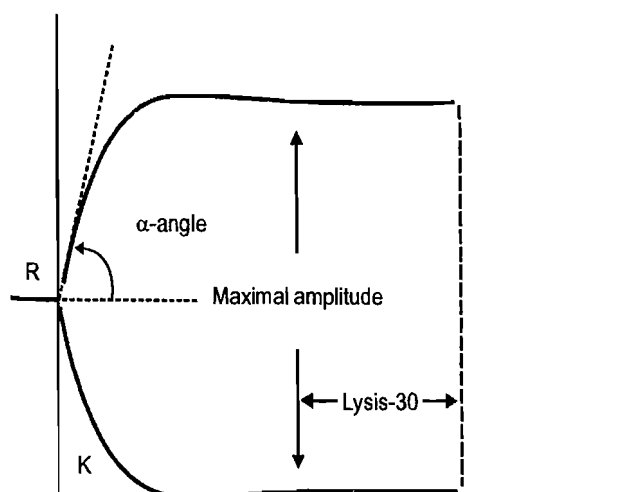
To get a more accurate picture of the hemostatic status in such patients, viscoelastic assay is imperative. Thromboelastography (TEG) and rotational thromboelastometry

(ROTEM) are two methods of viscoelastimetric assay used widely these days. Different steps of the clot formation, clot lysis, physical properties of clot, like clot strength, and contribution of different coagulation proteins as well as fibrinolytic activities can be assessed in a single study with a graphical as well as numerical representation (Table 1 and Fig. 1). A pin suspended from a torsion wire is dipped into a cup-containing blood sample of 0.36 mL at 37°C temperature, and the torsion wire is attached with a mechanical-electrical

TABLE 1 Interpretation of thromboelastography

TEG measurement	Definition	Interpretation and suggested replacement product
Reaction time (R time) in minute	Time from initiation of coagulation to fibrin formation	Prolonged R represents delayed initiation of coagulation due to deficiency of clotting factors. Suggest fresh frozen plasma
Kinetic time (K time) in minute	Time from formation of fibrin to 20 mm of clot strength	Prolonged K represents deficiency of fibrinogen. Suggest cryoprecipitate
Alpha-angle in degrees	Rate of fibrin formation	Decreased angle represents slow rate of clot formation due to deficiency of fibrinogen. Suggest cryoprecipitate
Maximum amplitude (MA) in mm	Maximum clot strength	Decreased MA represents decreased clot strength due to decreased platelet count or function. Indicates platelet transfusion
Lysis-30 (Ly-30)%	Fibrinolysis 30 minutes after MA	Increased Ly-30 suggests more rapid fibrinolysis and may be amenable to aminocaproic acid or tranexamic acid to prevent clot lysis

TEG, thromboelastography.



R, reaction time; K, kinetic time.

FIG. 1: Schematic representation of thromboelastogram

transducer. With the formation of the clot, the rotation of the pin is changed accordingly that produces mechanical energy, converted to electrical energy by the transducer. A computer system then represents this electrical input to a graphical and numerical output. By only seeing the graph's characteristic, the time of onset of clot formation, rapidity of clot formation, maximum strength of clot and the rate of clot, lysis can be easily assessed. This test is helpful clinically in deciding, if the patient requires any blood products and also which type of blood products. Thus by using TEG or ROTEM, inappropriate use of blood products is reduced. Transfusion decision by TEG results in the higher use of platelet and cryoprecipitate than blood or first frozen plasma (FFP). Thromboelastography done in ALF patients demonstrates a normal coagulation profile in 63% of cases and a hypercoagulable state in only 8% of cases.⁷ In advanced stage of cirrhosis, TEG reveals decreased maximum amplitude of clot indicating reduced clot strength due to thrombocytopenia and tendency toward anticoagulation, which is not seen in earlier stage. Thus, thrombocytopenia or asthenia is directly related to the chronicity and severity of liver disease as evidenced by TEG.

As TEG parameters are a reflection of the cumulative effect of hemostatic status, it can be used in predicting if patients with ALF or CLD have an increased risk of bleeding or not. In patients with ALF, if TEG shows an increased reaction (R) time, that indicates an increased risk of further bleeding, which may not be detected by insignificant change in international normalized ratio (INR) value between bleeding and nonbleeding groups.⁷ In cirrhotics, TEG can anticipate patients with high risk of bleeding from esophageal varices, even in those with normal traditional coagulation parameters.⁸ Despite the beneficial effects of TEG as stated earlier, some studies show very contradictory results that are still not explained well. A study by Kang et al. found TEG parameters to be matched well with conventional coagulation assays.⁹ However, a recent study by Stravitz et al. reveals contradictory results. They found prolonged R time correlates well with clinically evident thrombosis, thus indicating a hypercoagulable state.⁷ Thus further well-designed, randomized, and prospective trials are necessary for a stronger and better validation of TEG.

CLINICAL IMPLICATIONS

Bleeding

Patients of ALF rarely bleed. Bleeding is a more important problem in patients with CLD. It has been found that most episodes of bleeding in CLD are due to variceal bleeds in nearly 25–35% of cirrhotic patients.¹⁰ Nonvariceal bleeding is also not less common in these patients. It occurs in nearly 20% of decompensated cirrhotics.¹¹ Bleeding risk is also increased while doing invasive procedures like liver biopsy, thoracentesis, paracentesis, coronary angiography, large vein or arterial catheterization. Despite the wide array of tests

available, none can predict convincingly the risks of bleeding in liver failure. As stated earlier, infection, uremia, portal hypertension, and certain medications contribute further to the risk of bleeding. Thus, a prudent clinical approach is imperative while deciding on invasive interventions in these patients.

Disseminated Intravascular Coagulation and Accelerated Intravascular Coagulation and Fibrinolysis

As discussed earlier, dysregulated hemostatic mechanisms in liver disease often lead to a state almost resembling disseminated intravascular coagulation, which is known as AICE. Accelerated intravascular coagulation and fibrinolysis is due to a defect in synthesis of pro- and anticoagulants from hepatocytes and a hyperactive fibrinolysis, while in DIC the cause is activation of thrombotic pathway in small vessels that leads to an excessive consumption of coagulation factors and traumatic blood cell damage known as thrombotic microangiopathy. These two conditions so closely resemble each other that differentiation between the two is difficult. In both these conditions, there is hypofibrinogenemia. To distinguish them, clinical judgment is imperative to identify whether any predisposing factor is present to activate the cascade of DIC or not. Some laboratory findings may differentiate these two situations:

- Factor VIII generally remains normal or is increased in liver disease, while it is reduced in DIC
- D-dimer mostly remains normal or is mildly elevated in liver disease but it is markedly increased in DIC indicating ongoing active fibrinolysis.

Unfortunately, significant overlap may exist and complicate the diagnostic dilemmas.

Factor VIII:V ratio was found to predict mortality in paracetamol-induced ALF in one study. A ratio of <30 indicates a good prognosis while >30 correlated with high mortality.¹²

Most importantly, it is not uncommon to see a patient with liver disease who also has DIC due to the presence of risk factors like infection, sepsis or malignancy that activate the cascade of DIC.

Thrombosis

A few studies have indicated that patients with liver disease have a proclivity toward thrombosis, rather than bleeding.¹³ The thrombotic episodes mainly include deep vein thrombosis, portal vein thrombosis and pulmonary embolism (PE). Some studies reveal that portal vein thrombosis correlates well with the severity and chronicity of cirrhosis ranging from 1% in compensated cirrhosis to approximately 8–25% in decompensated cases posted for liver transplantation.¹⁴ Nery et al. found a different result. According to their study, there is no evidence that the development of portal venous thrombosis is responsible for further progression of liver

disease.¹⁵ Deep vein thrombosis and subsequent PE is seen in 0.5–8% of cases. Identifying which patient has a potential to bleed or who is a candidate for thrombotic episodes is challenging and most of the time remain unanticipated by laboratory parameters. International normalized ratio values do not have a correlation with such increased risk of thrombosis nor can its raised level indicate a protection against venous thromboembolism (VTE).¹⁶ Thus, recognizing this subgroup is an important consideration. Some risk factors like increased age, presence of malignancy, prolonged bed-ridden state, male gender, postmenopausal women with hormone therapy, associated comorbidities, poor nutritional status, and indwelling catheters indicate risks more toward thrombosis. Serum albumin level is found to be a suitable marker in identifying patients with thrombotic risk. Risk is increased to five times with albumin level <1.9 mg/dL.¹⁶

Medications to Avoid

Due to this complexity in hemostatic mechanism and also due to poor predictive ability of laboratory parameters, some drugs which either have increased bleeding risk or thrombotic risk should be better avoided until the benefits of those clearly outweigh the risk associated with them. Commonly used analgesics, antipyretics, and over-the-counter nonsteroidal anti-inflammatory drugs should be avoided. Another important consideration is antiplatelet agents like aspirin or P2Y₁₂ inhibitors (e.g., clopidogrel). If cardiovascular indications like recent myocardial ischemia or percutaneous transluminal coronary angioplasty suggests beneficial effect of antiplatelet agents, they should be continued, accepting a higher-bleeding risk. Any hemostatic agent should also be deferred unless there is any life-threatening bleeding.

MANAGEMENT

Venous Thromboembolism Prophylaxis

Liver disease patients, despite having increased PT, APTT, and INR levels are at an increased risk of VTE, but whether one should initiate antithrombotic prophylaxis is controversial. A few studies also suggest that VTE prophylaxis is underprescribed due to misconception that these patients are autoanticoagulated and the condition is often ignored by falsely elevated anticoagulation markers. Recently, a randomized controlled trial was done in CLD patients with mean Model for End-Stage Liver Disease score of 16.2. They were compared between unfractionated heparin and low-molecular weight heparin. The study found that subsequent bleeding risk or heparin-induced thrombocytopenia is not significantly increased.¹⁷ Efficacy of mechanical sequential compression device has not been evaluated on a large scale, but is thought to be ineffective treatment option in the presence of peripheral edema. Pharmacological

treatment may also be complicated by presence of renal failure. So, prophylaxis depends mostly on clinician's discretion and experience. However, in the presence of severe thrombocytopenia (platelet count $<50,000/\mu\text{L}$), active bleeding or high risk varices (e.g., red wale marks and stigmata of recent bleeding) and heparin prophylaxis should be avoided.

Venous Thromboembolism Therapy

Therapeutic intervention in the setting of CLD is complicated due to increased risk of bleeding and also difficulty in monitoring the adequacy due to elevated level of baseline PT, APTT, and INR. Moreover, there is still no recommendation regarding specific anticoagulant, dose, and duration of therapy. Thus, before initiating therapy, one has to balance the risk and benefit of anticoagulation considering the presence or absence of variceal bleeding. Check endoscopy should be done to identify presence of varices and its severity before initiating therapy. If varices are present, placement of inferior vena cava (IVC) filter may be a better option. If peripheral veins and involving lower limbs are present, one has to keep in mind that IVC filter also has thrombogenic potential. But recent advent of removable filter, which may be used temporarily, may be considered. If PE is present, therapy should be initiated after stabilizing varices. In patients without significant varices, therapy may be done with either vitamin K antagonist like warfarin or direct thrombin/factor Xa inhibitors like dabigatran, apixaban, rivaroxaban, and endoxaban.¹⁸ The duration of therapy depends on clinical judgment as no recommendations exist.

Pulmonary Venous Thromboembolism Prophylaxis

Pulmonary venous thromboembolism (PVT) risk is increased simultaneously with disease severity.¹⁹ Risk is also increased by presence of hepatic malignancy or associated with inherited coagulopathy like thrombophilia, factor V Leiden mutation. Prophylaxis mainly focuses on optimizing hepatic function, reducing portal venous pressure, and augmenting portal flow by reducing venous stasis. Prophylactic use of anticoagulant is not always necessary for PVT unless other reasons of anticoagulant therapy coexist. In some retrospective studies, it was observed that use of anticoagulants effectively hasten the recanalization rate.²⁰ Various societies do not make any recommendations regarding use of anticoagulants in PVT in cirrhotics.²¹

Therefore, treating patients with thrombosis depends on clinical discretion. There is no clear cut evidence till date regarding which anticoagulants should be used in what doses and for how long. Due to preexisting abnormalities in INR, dosing and monitoring is also difficult. Before initiating medications, patients should be screened for

esophageal varices and if present it should be stabilized first or prophylaxis of variceal bleed should be initiated either with band ligation or nonselective β -blockers. It decreases risk of bleeding in PVT patients while anticoagulants are given.²² Enoxaparin can be given at either a dose of 1 mg/kg subcutaneously twice daily or 1.5 mg/kg once daily.

Bleeding

Bleeding in patients with liver disease is mostly due to portal hypertension-causing variceal rupture rather than hemostatic abnormalities.¹⁰ However, nonvariceal bleeding also comprised of 20% of cases in a study by Shanane et al. The reasons are portal hypertensive gastropathy, gastric vascular ectasia, peptic ulcer for upper gastrointestinal (UGI) bleed and portal hypertensive colopathy for lower gastrointestinal bleed. Other rare causes of UGI bleed are Dieulafoy's lesion, Mallory-Weiss syndrome, and portal hypertensive enteropathy. Bleeding can also occur during interventions as stated earlier. As bleeding risk cannot be anticipated by only relying on INR, often the intervention is delayed. Possibilities of having vitamin K deficiency are to be kept in mind while dealing with such patients. Decision of blood product transfusion is better made on the basis of TEG/ROTEM as unnecessary use of blood products is reduced.

Vitamin K Deficiency

Chronic liver disease associated with vitamin K deficiency is very common due to alcohol intake, malnutrition, cholestasis, diarrhea, or antibiotic use. When it is suspected, vitamin K should be replaced. In an actively bleeding patient the dose is 10 mg intravenously at a rate not >1 mg/min. When bleeding is minor the oral route is preferred, if there is no abnormality in intestinal absorption. The dose is 10 mg/day for 3 days.

Cryoprecipitate and First Frozen Plasma

Though blood product transfusion is better guided by TEG/ROTEM for active or poorly controlled bleeding when blood product transfusion is an emergency, cryoprecipitate is transfused at a dose of one bag/10 kg body weight. First frozen plasma can also be given. Cryoprecipitate offers less volume load than FFP for same amount of fibrinogen replacement. The target fibrinogen level is at least 100–120 mg/dL.²³ Some clinicians also prefer to give cryoprecipitate or FFP even when fibrinogen level is >120 mg/dL. Risk of variceal bleeding should be considered due to increased portal venous flow secondary to volume overload even if varices are not the primary site of bleeding. If the bleeding is still not controlled then prothrombin complex concentrate or a factor VIIa may be considered on the basis of clinical judgment, but should not be used aggressively due to increased chance of thrombosis.

Red Blood Cell and Platelets

Blood should be transfused with target hemoglobin of 7 g%. Packed red blood cell should be used rather than using whole blood. Higher target of hemoglobin may be considered in patients with cardiovascular disease.

According to American Association for the Study of Liver Diseases guideline, platelet should be transfused to maintain a platelet count above 50,000–60,000/ μL .²⁴ In case of active, severe, or central nervous system bleeding, platelets should be maintained above 100,000/ μL . Need for platelet transfusion may be guided by the TEG study to decrease inadvertent usage. During liver biopsy, platelet should be maintained above 60,000/ μL , as a small study indicates greater chance of bleeding during liver biopsy if platelet counts falls below that level.²⁴ As hyperfibrinolysis is a well-known complication in liver disease, antifibrinolytic like tranexamic acid (TXA) or epsilon aminocaproic acid may be considered for active bleeding. A Cochrane review also supports the use of TXA in UGI bleeding. Tranexamic acid is also considered as safe and effective antifibrinolytic agent in liver transplant patients.²⁵ Though these agents may be used either orally or intravenously or soaked in gauze during dental extraction procedures, but the dose in liver disease has not been established and it is used on the basis of clinical response.

CONCLUSION

In liver disease, due to complex and unpredictable alterations of pro- and anticoagulant proteins, a new hemostatic state arises known as rebalanced hemostasis. Conventional laboratory parameters of coagulation may mislead clinician in predicting risk of bleeding or thrombosis as well as anticoagulant dosing and monitoring. Thromboelastography/ROTEM helps more judicious use of anticoagulants or antifibrinolytic agents. In volume-overloaded patients, cryoprecipitate is better option than FFP as volume overload also worsens portal hypertension. Platelet transfusion should be considered during invasive procedures, as thrombocytopenia or thrombosthenia is inevitable association in liver disease. Life-threatening thrombotic events should be treated prudently on case-by-case basis. Still, there are many unanswered questions and large scale trials are needed to establish better evidence for management of these difficult clinical situations.

REFERENCES

1. Tripodi A, Primigani M, Chantarangkul V, et al. An imbalance of pro vs anticoagulation factors in plasma from patients with cirrhosis. *Gastroenterology*. 2009;137(6):2105-11.
2. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol*. 2008;48(6):1000-7.
3. Bernerd B, Granze JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infection in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology*. 1999;29(6):1655-61.
4. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of Von Willibrand Factors in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology*. 2006;44(1):53-61.
5. Agarwal S, Joyner KA Jr, Swaim MW. Ascites fluid as a possible origin for hyperfibrinolysis in advanced liver diseases. *Am J Gastroenterol*. 2000;95(11):3218-24.
6. Lisman T, Bakhtari K, Adelmeijer J, et al. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. *J Thromb Haemost*. 2012;10(7):1312-9.
7. Stravitz RT, Lisman T, Luketic VA, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol*. 2012;56(1):129-36.
8. Chau TN, Chan YW, Patch D, et al. Thromboelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. *Gut*. 1998;43(2):267-71.
9. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. *Anesth Analg*. 1985;64(9):888-96.
10. Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. *N Engl J Med*. 2001;345(9):669-81.
11. Shah NL, Northup PG, Caldwell SH. A clinical survey of bleeding, thrombosis, and blood product use in decompensated cirrhosis patients. *Ann Hepatol*. 2012;11(5):686-90.
12. Pereira LM, Langley PG, Hayllar KM, et al. Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure: relation to other prognostic indicators. *Gut*. 1992;33(1):98-102.
13. Tripodi A, Primignani M, Lemma L, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. *Hepatology*. 2010;52(1):249-55.
14. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut*. 2005;54(5):691-7.
15. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology*. 2015;61(2):660-7.
16. Northup PG, McMahon MM, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol*. 2006;101(7):1524-8.
17. Intagliata NM, Henry ZH, Shah N, et al. Prophylactic anticoagulation for venous thromboembolism in hospitalized cirrhosis patients is not associated with high rates of gastrointestinal bleeding. *Liver Int*. 2014;34(1):26-32.
18. Intagliata NM, Maitland H, Northup PG, et al. Treating thrombosis in cirrhosis patients with new oral agents: ready or not? *Hepatology*. 2015;61(2):738-9.
19. Buresi M, Hull R, Coffin CS. Venous thromboembolism in cirrhosis: a review of the literature. *Can J Gastroenterol*. 2012;26(12):905-8.
20. Condat B, Pessione F, Denninger MH, et al. Recent portal or mesenteric thrombosis: increased recognition and frequent recanalization on anticoagulation therapy. *Hepatology*. 2000;32(3):466-70.
21. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology*. 2009;49(5):1729-64.
22. Amitrano L, Guardascione MA, Menchise A, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. *J Clin Gastroenterol*. 2010;44(6):448-51.
23. Shah NL, Intagliata NM, Northup PG, et al. Procoagulant therapeutics in liver disease: a critique and clinical rationale. *Nat Rev Gastroenterol Hepatol*. 2014;11(11):675-82.
24. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology*. 2009;49(3):1017-44.
25. Molenaar IQ, Wamaer N, Groen H, et al. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant*. 2007;7(1):185-94.

Permissive Underfeeding in Intensive Care Unit: Current Status

Saswati Sinha

INTRODUCTION

Catabolism is almost inevitable in the seriously ill patient leading to protein breakdown, negative nitrogen balance, and a loss of lean body mass up to 15–20% during the first few days of intensive care unit (ICU) stay particularly in patients with multiorgan failure thereby negatively affecting outcome. Patients during critical illness are unable to feed orally adequately due to both the disease and the therapy and hence the need to provide nutrition enterally or parenterally to mitigate these deficits. Several studies have shown that cumulative nutritional deficits are associated with adverse outcomes in critically ill patients. On the other hand, overfeeding or excessive caloric intake has been associated with hyperglycemia, insulin resistance, hepatic steatosis, increase in mechanical ventilation and mortality.¹ For decades, it has been dogmatically accepted that nutritional support must provide 100% of the estimated caloric requirement at all times. There is a lack of consensus regarding the caloric target for feeding critically ill patients.

TERMINOLOGY

Permissive underfeeding is the provision of lower than goal nutritional intake which aims at preserving gut mucosal integrity, preventing bacterial translocation, allowing better absorption of nutrients simultaneously alleviating the problems associated with overfeeding. Several terminology have been used interchangeably such as trophic or trickle feeding, which amounts to feeding at 10–20 mL/h (500–1,000 kcal/day) or hypocaloric feeding, which usually refers to lower than recommended or target energy intake.

RANDOMIZED CONTROLLED TRIALS ON PERMISSIVE UNDERFEEDING IN INTENSIVE CARE UNIT

1. In 2011, Arabi et al. randomized 240 medical-surgical ICU patients to permissive underfeeding or

target feeding (calorie target: 60–70% vs. 90–100%, respectively). The standard calorie requirement was estimated using the Harris-Benedict equation taking into account stress factors. Caloric intake also included intravenous dextrose and propofol. Protein requirement was calculated as 0.8–1.5 g/kg as per disease and underlying condition. There was no difference in the primary outcome of 28 day all-cause mortality—18.3% in the permissive underfeeding group versus 23.3% in target feeding group [relative risk (RR)—0.79; confidence interval (CI)—0.48–1.29, $p = 0.34$]. Hospital mortality was lower in permissive underfeeding group (30.0% vs. 42.5% RR—0.71, 95% CI 0.50, 0.99; $p = 0.04$). There was no difference in ICU length-of-stay (LOS) or mechanical ventilation days, infections or need for renal replacement therapy.²

2. In 2012, Rice et al. randomized 1,000 adult patients with acute lung injury within 48 hours of requiring mechanical ventilation to trophic or full enteral feeding for first 6 days or extubation or death. After 6 days, patients who remained ventilated were shifted to full feeding protocol. Trophic feed was defined as 10–20 kcal/h. Full feeding rates were estimated as 25–30 kcal/kg/day of nonprotein calories and 1.2–1.6 g/kg/day of protein. There was no difference in ventilator-free day (VFD) to day 28, which was the primary endpoint (4.9 vs. 15). Apart from fewer incidences of gastrointestinal (GI) intolerance, hypocaloric feeds did not reduce mortality, infections, or LOS [Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome (EDEN) trial].³
3. In 2014, Petros et al. randomized 100 critically patients within 24 hours of ICU admission to normocaloric (100% daily energy expenditure) or hypocaloric (50% daily energy expenditure) for first 7 days of ICU stay. Primary outcome—incidence of nosocomial infections occurred more in hypocaloric group but insulin demand and GI intolerance were lower. Intensive care unit and hospital mortality were unchanged.⁴

4. In 2014, Charles et al. aimed at determining, if hypocaloric feeding could reduce surgical infections. A total of 83 patients were randomized to eucaloric versus hypocaloric feeding. Caloric intake was estimated as 25–30 kcal/kg/day in eucaloric and 12.5–15 kcal/kg/day in hypocaloric group. Protein intake 1.5 g/kg/day was uniform in both groups. There was no difference in any endpoints including infections, glucose control, ICU/hospital LOS, or mortality even after stratifying for gender, admission diagnosis, infection site, or causative organism.⁵
5. In 2015, Arabi et al. attempted to readdress this issue and randomized 894 critically ill patients to permissive underfeeding (40–60% of calculated calorie requirements) versus standard enteral feeding (70–100% of calculated energy requirements) while maintaining similar protein intake for up to 14 days. Protein supplements were administered in the hypocaloric group to maintain the balance. Primary outcome was 90-day mortality. This trial too found no difference [27.2 vs. 28.9% patients died, relative risks (RR)–0.94; 95% confidence interval (CI) 0.76–1.16; $p = 0.54$]. Feeding intolerance, infection, diarrhea as well as ICU and hospital LOS were also similar (PERMIT trial).⁶

With the aforementioned studies in view, should the concept of permissive underfeeding change our day-to-day clinical practice and several issues need consideration?

- Numerous studies have shown a positive correlation between protein and energy intake and clinical outcomes.

Alberda et al. studied 2,884 patients from 167 ICUs across 37 countries for maximum 12 days in ICU. Body mass index was used to stratify premorbid nutritional status. An increase of 1,000 kcal/day decreased 60-day mortality (RR–0.76, 95% CI 0.61–0.95, $p = 0.014$) and increased VFDs (3.5 VFD, 95% CI 1.2–5.9; $p = 0.003$). The benefit was seen in patients with body mass index <25 or >35 with similar relation to protein intake⁷

- Daren Heyland et al. have highlighted that not all ICU patients have the same nutritional risk and propose that patients with higher nutritional risk be identified. The Nutrition Risk in Critically ill (NUTRIC) score is a practical, bedside tool using parameters—age, APACHE II (Acute Physiology and Chronic Health Evaluation (APACHE II), SOFA (Sequential Organ Failure Assessment), number of comorbidities, days from hospital to ICU admission and interleukin (IL)-6 (optional). Higher scores (6–10, 5–9 if IL-6 available) are associated with worse clinical outcomes (mortality and ventilation) and identify patients who would benefit from aggressive nutrition therapy⁸

Most of the trials on permissive underfeeding have included younger patients who were likely to have a normal NUTRIC score and excluded high-risk patients, which would limit extrapolation of the results.

- Another major caveat being most trials have calculated requirements based on body weight, which may be actual or ideal body weight which are mostly approximation rather than estimation by indirect calorimetry, which is not universally available. A recent pilot trial has shown that closely supervised nutritional delivery based on repeated energy measurements was achievable and might be associated with a lower hospital mortality⁹
- There is a paucity of long-term outcomes in trials on hypocaloric feeds. Needham et al. presented the 1 year follow up of EDEN trial and showed that initial nutritional adequacy in ICU may be linked with better physical outcomes at 1 year,¹⁰ which has also been confirmed by other larger observational studies.

CONCLUSION

The importance of nutrition in ICU is indisputable, however, there is controversy regarding the optimum dosage. No single prescription fits all and with present data available, permissive underfeeding might offer some benefits like attenuating infection risk and some short-term outcomes, but it can still not be the norm for all ICU patients and it is prudent to tailor nutrition based on premorbid status and aim at optimizing protein and calorie intake, especially for patients at nutritional risk.

REFERENCES

1. Klein CJ, Stanek GS, Wiles CE 3rd. Overfeeding macronutrients to critically ill adults: metabolic complications. *J Am Diet Assoc.* 1998;98:795–806.
2. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr.* 2011;93:569–77.
3. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA.* 2012;307:795–803.
4. Petros S, Horbach M, Seidel F, et al. Hypocaloric vs normocaloric nutrition in critically ill Patients: A prospective randomized pilot trial. *J Parenter Enteral Nutr.* 2016;40:242–9.
5. Charles EJ, Petroze RT, Metzger R, et al. Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: A randomized controlled trial. *Am J Clin Nutr.* 2014;100:1337–43.
6. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med.* 2015;372:2398–408.
7. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med.* 2009;35:1728–37.
8. Heyland DK, Dhaliwal R, Jiang X, et al. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care.* 2011;15:R268.
9. Singer P, Anbar R, Cohen J, et al. The Tight Calorie Control Study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med.* 2011;37:601–9.
10. Needham DM, Dinglas VD, Morris PE, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. *Am J Respir Crit Care Med.* 2013;188:567–76.

Making Parenteral Nutrition Safer

Subhash Todi, Sadanand S Kulkarni

INTRODUCTION

Nutrition is fundamental to health. While in most patients, an adequate dietary intake can be ensured by providing adequate enteral nutrition (EN), in others whom nutritional requirements cannot be met through enteral route, clinical nutrition support involving parenteral nutrition (PN) becomes indispensable. Parenteral nutrition is the intravenous infusion of nutrients directly into the systemic circulation, bypassing the gastrointestinal (GI) tract.¹ It serves as an important therapeutic modality that is used in adults, children, and infants for a variety of indications. The appropriate use of this complex therapy is, however, essential to maximize clinical benefits while minimizing the potential risk for adverse events and complications, which may occur both because of the PN admixture itself and the processes within which it is used.² The safe practice guidelines have been derived by different clinical societies in terms of PN.³

Appropriate and safe prescribing/ordering of PN is a critical first step and an essential component of the PN-use process. The prescriber should be well versed in the appropriate indications for PN as well as vascular access devices (peripheral and central) and their associated complications.⁴ An extensive examination of the patient is required to decide on possible indications and contraindications for PN and to adequately calculate nutrient requirements. This should comprise underlying and preexisting diseases and therapies, the condition of the GI tract, possibilities for oral and/or enteral food intake, the venous access, nutritional status, and laboratory parameters. Generally, PN is indicated for all patients who are malnourished or at risk of malnutrition and who cannot be fed adequately and/or safely via the oral/enteral route and those who have a nonfunctional, inaccessible or perforated GI tract.^{1,5} Also, PN should be considered

to supplement or replace enteral tube feeding to avoid malnutrition due to insufficient or absent EN.^{1,6}

FACTORS NEED TO BE CONSIDERED TO ENSURE SAFETY OF PARENTERAL NUTRITION

Osmolarity/Osmolality

One of the most important factors, which should be taken into consideration to provide safe PN to hospitalized patients is the osmolarity of the PN solution. Osmolarity is a measure of the osmotically active particles in the solute (osmoles) per liter of solution. It has been suggested that PN with an osmolarity of up to 900 mOsm/L can be safely infused peripherally. The administration of PN via a peripheral vein, often referred to as peripheral PN (PPN), is limited by tolerance to the concentrated macronutrient formula and high fluid volumes. The most significant complication limiting the tolerance of PPN is the development of thrombophlebitis. As characterized by redness, burning sensation, and rapid thrombosis. The incidence of thrombophlebitis is related to the osmotic content of the infused formula as well as the infusion rate. Dextrose and amino acids are significant contributors of solution osmolarity.⁷ It is important to note that lipid emulsions are isotonic with blood and exert a soothing effect on the veins. Therefore, PN admixtures-containing lipid emulsions are less hypertonic than emulsions-based solely on glucose as an energy source, and, consequently, more suitable for PPN.¹ Peripheral PN offers an easy-to-use and, if handled adequately, safe method for feeding patients in need of PN for a limited duration of 7–10 days. Peripheral PN is also indicated in patients with a moderate malnutrition status with lack of central venous access, and when a central venous PN is not justified due to a negative risk-benefit ratio (catheter sepsis or bacteremia).

Multiple Single Bags or Single-bag Multichambered Parenteral Nutrition

Parenteral nutrition formulations in multichamber bags often referred to as "premixed" although they require mixing before administration have been recommended as safer and more efficient delivery systems for macronutrients and micronutrients compared with traditional single-bag formulations.⁷

Non-nutrient Medication in Parenteral Nutrition

When maximizing the safety in PN, it is essential to understand the implications of the use of PN admixture as a vehicle for non-nutrient medication delivery. It has been recommended that non-nutrient medication should be included in PN admixtures only when supported by pharmaceutical data describing physicochemical compatibility and stability of the additive medication.^{8,9}

Taking into account all of the contents, the stability and compatibility of PN admixtures are pharmaceutically complex in the absence of drug additives.^{8,9}

Given this complexity, caution is required before introducing substances (including medication) not known to be compatible and stable with PN. The inclusion of non-nutrient medication with PN admixtures, however, is not generally recommended.²

Central Venous Catheters and Care

In the planning of PN, the proper choice, insertion, and care of the venous access are of outstanding importance.¹⁰ Parenteral nutrition solutions are administered either via a central venous catheter or peripheral venous cannulas.¹¹ When choosing the appropriate route of access, the following criteria should be taken into consideration:^{1,10,11}

- Condition of the patient (type of illness, current state of health, etc.)
- Accessibility of the venous system
- Composition of the infused solution and amount of energy to be administered
- Osmolarity of PN products
- Planned duration of PN (short-term or long-term).

Indications for Central Venous Access

According to the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), central venous access is indicated in the majority of patients with the following indications:¹⁰

- Need for long-term (>1 months) nutritional support
- Patients with poor peripheral veins
- Need for hyperosmolar solutions (osmolarity >850 mOsm/L)
- Glucose concentration >125 g/L¹

- High-nutrient requirements
- Severe fluid restriction
- Administration of solutions with pH <5 or pH >9
- Need for multiple lumen intravenous treatment.

Catheter Care

In order to prevent catheter-related infections, proper insertion site care has been considered one of the most important measures. Strict hand hygiene and skin antisepsis during placement and handling as well as regular monitoring of the exit site are prerequisites for minimizing microbial colonization. Flushing maintains catheter patency and reduces fibrin or thrombus formation. It has been suggested though not commonly practiced, that very low doses (1 mg/day) of warfarin can protect against thrombosis in patients with long-term central venous access.¹²

European Society for Clinical Nutrition and Metabolism has given following recommendations to reduce the risk of catheter-related infections:¹⁰

- Use of single-lumen catheters
- Appropriate choice of insertion site
- Use of 2% chlorhexidine as skin antiseptic
- Disinfection of hubs, stopcocks, and needle-free connectors
- Regular change of administration sets.

Monitoring

It is important to note that the use of PN is not associated with increased mortality compared to EN. The risk of PN-associated complications such as refeeding syndrome, hyperglycemia, bone demineralization, and catheter infections can be minimized by careful and systematic monitoring of clinical and laboratory parameters.^{13,14} During the early phase of PN, particularly in critical illness, biochemical monitoring (blood glucose, urea, electrolytes, and blood gases) should be performed daily. The full set of laboratory parameters should then be repeated 2-3 times a week after reaching the estimated or tolerated nutritional requirements. For stable home PN patients, the intervals between measurements may be extended further. Regular monitoring of PN can result in reduced complications and reduced costs.^{15,16}

CONCLUSION

Parenteral nutrition (parial, supplemental or total) is an integral part of modern nutrition care in intensive care unit. A safe delivery of this modality needs to be ensured by the multidisciplinary team comprising of physician, nurses, nutritionist and pharmacist. Indications and contraindication of such intervention, with risk benefit ratio should be carefully considered for individual patient. A proper modality and vascular access should be chosen. Careful monitoring of patients on PN should be done.

Last but not the least, timing initiation and termination of PN should be carefully based on available evidence and guideline recommendations.

REFERENCES

1. NICE: National Collaborating Centre for Acute Care. Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition. Methods evidence and guidance. London. 2006.
2. Mirtallo JM. Consensus of parenteral nutrition safety issues and recommendations. JPEN J Parenter Enteral Nutr. 2012;36:62S.
3. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28: S39-S70.
4. Boitano M, Bojak S, McCloskey S, et al. Improving the safety and effectiveness of parenteral nutrition: results of a quality improvement collaboration. Nutr Clin Pract. 2010;25:663-71.
5. Rothaermel S, Bischoff SC, Bockenhimer-Lucius G, et al. Ethical and legal points of view in parenteral nutrition—guidelines on parenteral nutrition chapter 12. Ger Med Sci. 2009;7:Doc16.
6. Kreymann KG. Early nutrition support in critical care: a European perspective. Curr Opin Clin Nutr Metab Care. 2008;11:156-9.
7. Boullata JJ, Gilbert K, Sacks G, et al. A.S.P.E.N. Clinical Guidelines: Parenteral Nutrition. Ordering, Order Review, Compounding, Labeling, and Dispensing. J Parent Ent Nutr. 2014;38:334-77.
8. Washington C. The stability of intravenous fat emulsions in total parenteral nutrition mixtures. Int J Pharm. 1990;66:1-21.
9. Manning RJ, Washington C. Chemical stability of total parenteral nutrition mixtures. Int J Pharm. 1992;81:1-20.
10. Pittiruti M, Hamilton H, Biffi R, et al. ESPEN Guidelines on Parenteral Nutrition: Central Venous Catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365-77.
11. Jauch KW, Schregel W, Stanga Z, et al. Access technique and its problems in parenteral nutrition—Guidelines on Parenteral Nutrition, Chapter 9. Ger Med Sci. 2009;7:1-18.
12. Krzywda EA, Edmiston CE. Parenteral Nutrition Access and Infusion Equipment. In: Merritt RJ (Eds). A.S.P.E.N. Nutrition Support Practice. Silver Spring, MD: A.S.P.E.N., 2005. Pp. 90-6.
13. Hartl W, Jauch KW, Parhofer K, et al. Complications and monitoring—guidelines on parenteral nutrition chapter 9. Ger Med Sci. 2009;7:Doc 17.
14. Allison SP, Cynober L, Stanga Z, et al. Monitoring of nutritional support. In: Sobotka L (Eds). Basic in Clinical Nutrition. Prague, Galen: 2011. Pp. 419-32.
15. Sobotka L, Wanten G, Camilo ME. Metabolic complications of parenteral nutrition. In: Sobotka L (Eds). Basics in Clinical Nutrition. Prague: Galen: 2011. pp. 411-7.

Autophagy: Relevance to Critical Care

Subhash Todi, Sriram Sampath

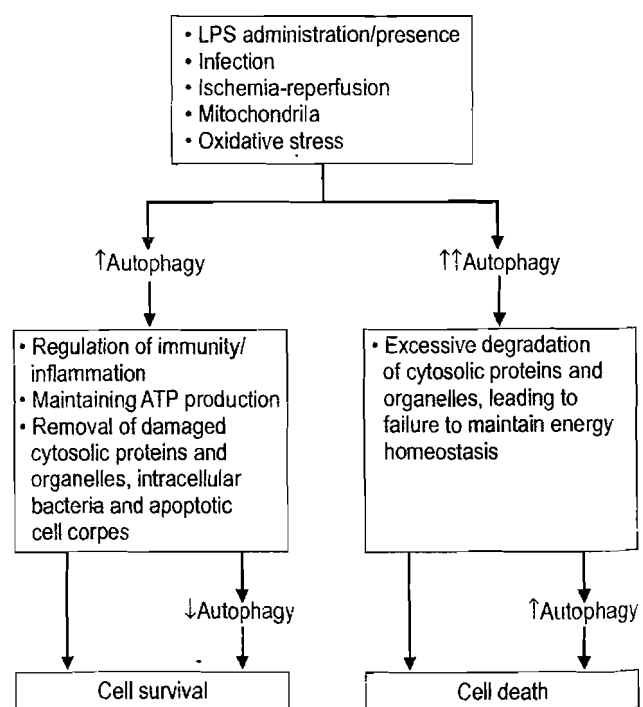
INTRODUCTION¹

Until now the field of critical care research was focused on identifying mechanisms of cellular injury by infection, inflammation, trauma, ischemia reperfusion, etc. through dysregulated inflammatory response and strategies to modulate this response for a favorable outcome from an external or internal insult. Not much emphasis was placed on the mechanisms of cellular repair and recovery, e.g., autophagy, modulation of which has attracted major attention of scientific community leading to award of Nobel Prize in Medicine in 2016 to Yoshinori Ohsumi for his work in this field. Defective autophagic processes seem to play a major role in infection, recovery from illness, nutrition, muscle metabolism all of which play a pivotal role in critically ill patient. Moreover, this phenomenon also plays an important role in development of cancer, autoimmune diseases and neurodegenerative diseases.¹ This chapter will briefly describe the phenomenon of autophagy and its relevance to critical illness particularly in the field of nutrition support where this concept has been applied from “bench to bedside”.

MECHANISM OF AUTOPHAGY^{2,3} (FLOWCHART 1)

All eukaryotic organisms have two methods of cell degradation—proteasomic and lysosomic. The proteasomic pathway is more important in amino acid homeostasis during the fed and healthy state. On the other hand, lysosomal pathway plays a major role in tissue homeostasis through the phenomenon of autophagy during the conditions of stress and nutritional deprivation. Autophagy is also known as macroautophagy in order to differentiate it from other less important autophagic mechanisms like microautophagy and chaperone-associated autophagy. It is a mechanism by which cell repairs itself from damaged intracellular organelles like mitochondria, ribosomes, large proteins, endoplasmic

reticulum, and also to invading bacteria, viruses, and lipopolysaccharides which if left unscavenged will lead to cellular injury. This occurs by the fusion of lysosome to an autophagosome, which contain the intracellular organelle or invading organism. The proteolytic enzymes within the lysosome breaks down the organelle or the organisms into its various components, which is ultimately extruded out of the autophagosome-lysosome assembly to be recycled as the constituents of new organelles contributing to repair of the cell. Metaphorically, the autophagy process acts like a “recycle bin” of a desktop computer where unnecessary folders can be stored and utilized later on to prevent the computer from getting “crashed” due to overload. Autophagy acts as a quality-control mechanism inside the



LPS, lipopolysaccharide; ATP, adenosine triphosphate.

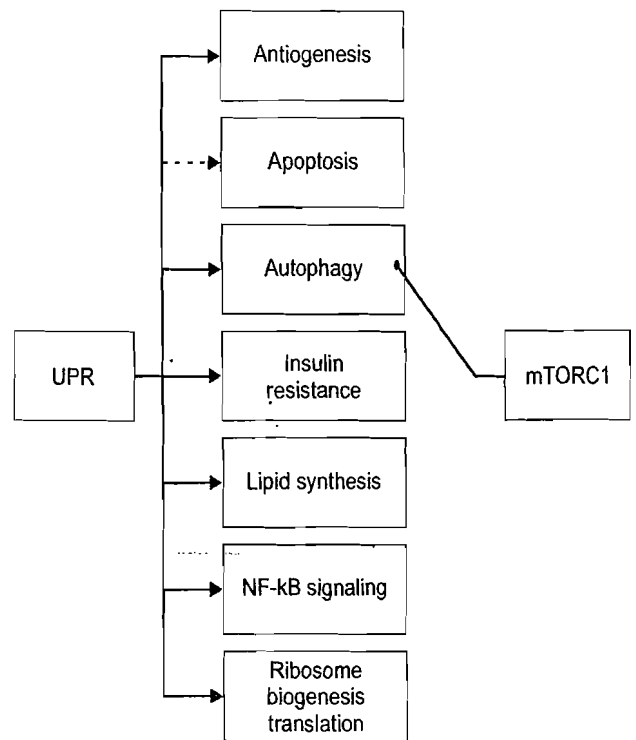
FLOWCHART 1: Autophagic pathway

cell by maintaining the important intracellular constituents especially for postmitotic cells like neurons and hepatocytes. This process is genetically determined through autophagy-targeted genes (ATG) and can be a nonspecific scavenger (macroautophagy) or specific for certain organelles and other products namely mitochondria (mitophagy), bacteria and viruses (xenophagy), protein aggregates (aggregatophagy), lipid (lipophagy), etc. Thus autophagy tends to maintain intracellular homeostasis in health and disease. The process of autophagy may become inhibited by excessive calories and protein, insulin, hyperglycemia and stimulated by stress, starvation, glucagon, rapamycin (sirolimus), and glutamine. Autophagy is distinct but related to apoptosis, in the sense that the latter is a phenomenon of natural cell death where cell chromatin and other organelles get condensed and ultimately taken up by macrophage leading to cell death (programed cell death type-1). On the other hand, unregulated autophagy may also lead to excessive destruction of intracellular organelles leading to apoptosis (programed cell death type-2). Thus autophagy can be protective in health and disease, but may also be destructive, if unregulated. Both autophagy and apoptosis are distinct from necrosis, which is a nonprogramed cell death secondary to inflammation due to impaired autophagic pathway or overwhelming insult, leading to cell swelling and destruction with release of proteolytic enzymes resulting in tissue and organ damage.

AUTOPHAGY AND CRITICAL CARE NUTRITION⁴⁻⁶ (FLOWCHART 2 AND FIG. 1)

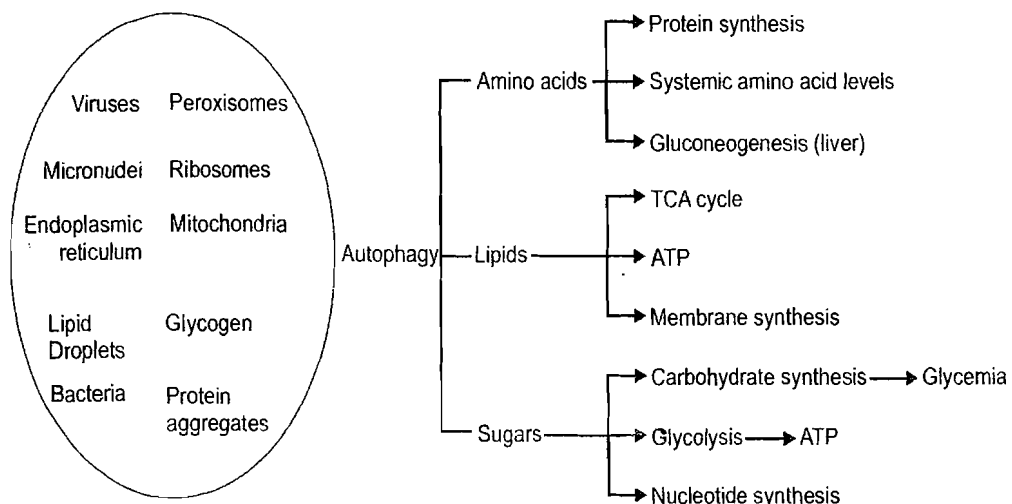
Critical illness invariably leads to decrease energy and protein intake in the face of increase protein catabolism and increased energy requirement leading to a state of protein calorie malnutrition. It is true that in many observational studies negative calories and nitrogen balance during early days of critical illness is associated with worse outcome.⁷ Although causality of this phenomenon cannot be established

by these trials and in fact nutrition intervention trials have not resulted in substantial improvement in mortality. Most of the nutrition guidelines emphasize early enteral nutrition for better outcome. Though the guidelines describe in details the procedural aspects of nutrition, benefit of feeding per se has not been established. Some guidelines also advocate early parenteral nutrition, if enteral route is not sufficient within 2-3 days of intensive care unit (ICU) stay. Moreover, early aggressive nutrition to attain calories and protein goals within 2-3 days has been advocated for a better outcome.⁸⁻¹⁰



UPR, unfolded protein response; mTORC1, mammalian target of rapamycin; NF-kB, nuclear factor kappa B.

FLOWCHART 2: Competing process of autophagy and mammalian target of rapamycin-1



ATP, Adenosine triphosphate; TCA, tricarboxylic acid.

FIG. 1: Autophagy in critical care nutrition

On the other hand, few studies have suggested that parenteral nutrition can be safely delayed for a week without harm and probably of some benefit, if enteral nutrition is not sufficient. Moreover, a strategy of hypocaloric or trophic feed for initial few days of enteral nutrition in mechanically ventilated patient was found to be noninferior to full feed. This has been studied in two randomized studies. In one trial, permissive underfeeding (60% of calories goal) significantly reduced hospital mortality.¹¹ In the EDEN study (Early Versus Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome) conducted in mechanically ventilated patient hypocaloric feed of 400 kcal (25% of the target) was compared to 1,300 kcal (85% of the target) till 6 days and was not found to be inferior in terms of mortality and morbidity.¹² In one of the largest randomized-controlled trial in critical care nutrition, more than 4,000 patients were randomized to early (<3 days) versus late (>7 days) administration of parenteral supplementation to enteral feeding, if found insufficient to deliver calories and protein goals. The mortality outcome was similar and morbidity outcomes were better in the late parenteral nutrition group.¹³

It has been consistently shown in studies comparing enteral versus parenteral nutrition that the infectious complications are lower in the enteral arm. The exact mechanism was unclear and was attributed to pro-inflammatory character of parenteral nutrition. It is equally possible that excessive calories, glucose, and protein load with parenteral nutrition, suppressed autophagy with impaired phagocytic function leading to increased infection rate in excessively fed patient. The underlying hypothesis of the hypocaloric feed trials is that full caloric feed or early parenteral nutrition during the early stage of critical illness impairs autophagy at the cellular level and results in more cellular injury. In fact, anorexia leading to restricted calories intake is a protective mechanism of any illness and circumventing it by forced early feeding is "going against nature" and may be harmful. Starvation predominantly protein deficiency stimulates the autophagic pathway, which helps in regenerating the essential amino acids from the breakdown products of intracellular organelles. Once the intracellular protein store is replenished, a negative feedback loop [mammalian target of rapamycin-I (mTORC1)] slows down the autophagic pathway, thus autophagy acts as a servo control mechanism of intracellular amino acid regulation in starvation and critical illness malnutrition.⁴ In experimental model autophagy, deficient cells fail to survive as they were not able to replenish essential protein constituents of antioxidant enzymes, respiratory cycle protein, etc. Autophagy suppression may lead to more accumulation of intracellular fat at the expense of protein due to the failure of recycling process.¹⁴

A contrary view to the protective role of autophagy has been put forward by some researchers.⁴ It has been suggested that autophagy is adaptive in less severe illness, but may

become maladaptive as severity of illness increases as the bioenergetics mechanism by autophagy alone is insufficient to maintain homeostasis in the absence of external nutrition. Excessive stimulation of autophagy may stimulate type-2 programmed cell death or lead to necrosis. Furthermore, glutamine which is a stimulant of autophagic pathway has not been found to improve outcome in recent clinical trials. It has been hypothesized that there is a balance between two mechanisms during health and disease with autophagy and mTOR system having feedback control over one another, the former is useful in preserving intracellular organelle and the latter in increasing utilization of external nutrition. Artificial nutrition need to address these two key balancing mechanism to prevent both over- and underfeeding.⁴

AUTOPHAGY AND CRITICAL CARE INFECTION¹

Innate immune system is constituted by monocyte, macrophage, and neutrophils for early recognition and containment of invading pathogen. Adaptive immune system constituted by T and B lymphocytes for antigenic memory and delayed response to invading pathogens and dendritic cells, which act as a link between innate and adaptive immunity are all regulated by the autophagy. Xenophagy is a subtype of autophagy through which many bacteria, which are predominantly intracellular and viruses fuse with autophagosome and degraded. These consist of *Salmonella*, *Shigella*, *Mycobacterium tuberculosis*, herpes virus, and chikungunya virus. This mechanism may be taken as a target for pharmacological manipulation, e.g., by promoting autophagy, blocking the microbial mechanisms for evading autophagy, promoting engulfment of intracellular pathogen by autophagosome, etc. In fact, vitamin D and sirolimus (formerly known as rapamycin), antitubercular drugs have been associated with promoting autophagy. Autophagy-dependent adaptive immune system may be used for the development of vaccines. Recent studies have shown linkage of autophagy genes with susceptibility to infections. This is a fertile field for future research in critical care infection.

AUTOPHAGY AND PERSISTENCE OF MULTIORGAN DYSFUNCTION AND DELAYED RECOVERY FROM CRITICAL ILLNESS

It is a common observation in critically ill that even after the initiating event, which may be infection, trauma or inflammation has been taken care of adequately by source control and anti-infectives the multiorgan dysfunction, which was initiated earlier persists in many patients. This implies a defect in recovery or repair mechanism leading to perpetuation of the organ damage. During the acute insult, damage to intracellular organelles (mitochondria and endoplasmic reticulum) need to be scavenged and new organelles need to be synthesized. In a knockout mice model,

where the autophagy gene ATG-7 was deleted, diminution of autophagy resulted and liver biopsy showed reduced number of autophagosome and increased damaged mitochondria accumulation. This was reflected by a phenotype of hepatomegaly and hepatocellular damage. In a similar model, skeletal muscle biopsy revealed decrease in myofibril size, vacuolation of myofibers, and reduction of muscle strength. As hyperglycemia and insulin are suppressors of autophagy, in a clinical study of intensive insulin therapy for strict glycemic control carried out in a surgical ICU, liver and skeletal muscle biopsies were performed postmortem in a selected group of patients from both arms of the trial, i.e., conventional therapy (liberal glucose) with tight control of glucose. In conventionally treated patient with liberal blood sugar both histologically and biochemically, there was evidence of deficient autophagy similar to that seen in the animal model. In the corresponding clinical study, persistent multiorgan dysfunction was also greater in conventional arm. Though insulin also decreases autophagy, it seems hyperglycemia was more detrimental than insulin therapy.

Removal of damaged mitochondria is a necessity for recovery from critical illness and presence of damaged mitochondria with accumulation of reactive oxygen species will prolong the illness. Mitophagy plays a key protective mechanism by acting as a "quality control" mechanism, getting rid of dysfunctional mitochondria followed by biogenesis of normal mitochondria. Excessive mitophagy can also be detrimental and thus can be a two-edged sword. In a rabbit model of burn injury, both hyperglycemic and hyperinsulinemic effect on autophagy was compared with hyperinsulinemic and normoglycemic state. It was shown that hyperglycemia was associated with diminished autophagy with more organ damage and perpetuation of organ damage, and this could be prevented by the use of rapamycin, which is a promoter of autophagy. Hyperglycemia affects autophagy by promoting mTOR pathway, which is a suppressor of autophagy. In normal situation, this mechanism is adaptive, but becomes maladaptive in critical illness. Further studies are needed in humans to know how blood sugar modulates the autophagy pathway and threshold of sugars at which this protective pathway is adversely affected.

AUTOPHAGY AND CRITICAL CARE-RELATED WEAKNESS

Autophagy is essential for maintaining muscle homeostasis in health and disease. In knockout mouse models, lack of autophagy was associated with accumulation of damaged mitochondria in the muscle, muscle degeneration, atrophy, and even more important observation was reversal of muscle damage after stimulation of autophagy postexercise.

Chaperone-associated autophagy pathway, a subtype of autophagy, is particularly important in disposing damaged organelles. Fasting and denervation-associated muscle wasting is exacerbated by excessive nutrition induced stimulation of autophagy.

CONCLUSION

The phenomenon of autophagy is a paradigm shift in critical care research and may explain the failure of mega-sepsis trials targeting cytokines, endotoxin, toll-like receptor, etc. to decrease mortality as this approach does not address the back end of the problem of cell repair. Moreover, the apparent beneficial effect of trickle feeding and harmful effects of early parenteral nutrition can also be explained by this mechanism. The future research in this field will target means of modulating, both upregulating and downregulating autophagy and providing some bedside markers to elucidate the status of autophagy in an individual patient.

REFERENCES

1. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. *N Engl J Med*. 2013;368:651-62.
2. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. *Cell*. 2011;147:728-41.
3. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. *Cell*. 2008;132:27-42.
4. McClave SA, Weijs PJ. Preservation of autophagy should not direct nutritional therapy: *Curr Opin Clin Nutr Metab Care*. 2015;18:155-61.
5. Schetz M, Casaer MP, Van den Berghe G. Does artificial nutrition improve outcome of critical illness? *Crit Care*. 2013;17:302.
6. Vanhorebeek I, Gunst J, Van den Berghe G et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *J Clin Endocrinol Metab*. 2011;96:E633-45.
7. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003;17:235-9.
8. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: intensive care *Clin Nutr*. 2006;17:210-23.
9. Taylor BE, McClave SA, Warren MM, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Crit Care Med*. 2016;44(2):390-438.
10. Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;17:387-400.
11. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr*. 2011;17:569-77.
12. Rice TW, Wheeler AP, Steingrub J, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;17:795-803.
13. Casaer MP, Mesotten D, Van den Berghe G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;17:506-17.
14. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. *Cell Metab*. 2009;17:507-15.

Nutrition Guidelines: What is New?

Rajesh Pande

INTRODUCTION

The 2016 American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine (ASPEN-SCCM) guidelines¹ give basic recommendations based on published evidence derived from various databases as well as expert opinion and target adult (≥ 18 years) critically ill patients expected to require a length-of-stay (LOS) >2 or 3 days in a medical or intensive care unit (ICU) surgical ICU (SICU). The current 2016 guidelines also address specific population groups with specific organ failure (pulmonary, renal and liver), acute pancreatitis, surgical patients [trauma, traumatic brain injury (TBI), open abdomen (OA) and burns], sepsis, postoperative major surgery, chronic critically ill and critically ill, obese patients. These guidelines advocate that nutrition therapy should be tailored to the individual patient. The current guidelines continue to use the GRADE methodology² (Grading of Recommendations, Assessment, Development and Evaluations) for classifying the supportive evidence like 2009 guidelines³ (Table 1).

NUTRITIONAL ASSESSMENT⁴

It was recommended to use Nutrition Risk in Critically ill (NUTRIC) score⁵ (Table 2) and Nutritional Risk Score (NRS 2002)⁴ (Table 3) to assess the nutritional status of critically ill

TABLE 1 GRADE classification

Quality	Definition
High	Further research is very unlikely to change our confidence in the estimate effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GRADE, Grading of Recommendations, Assessment, Development and Evaluations.

TABLE 2 NUTRIC score

NUTRIC score variables		
Variable	Range	Point
Age	<50	0
	50–75	1
	≥ 75	2
APACHE II	<15	0
	15– <20	1
	20–28	2
	≥ 28	3
SOFA	<6	0
	6– <10	1
	≥ 10	2
Number of comorbidities	0–1	0
	≥ 2	1
Days from hospital to ICU admission	0– <1	0
	≥ 1	1
IL-6	0– <400	0
	≥ 400	1

NUTRIC score scoring system: If interleukin-6 available

Sum of points	Category	Explanation
6–10	High score	<ul style="list-style-type: none"> Associated with worse clinical outcomes (mortality and ventilation) Most likely to benefit from aggressive nutrition therapy
0–5	Low score	<ul style="list-style-type: none"> These patients have a low nutrition risk

NUTRIC score scoring: If no interleukin-6 available

Sum of points	Category	Explanation
5–9	High Score	<ul style="list-style-type: none"> Associated with worse clinical outcomes (mortality and ventilation) Most likely to benefit from aggressive nutrition therapy
0–4	Low score	<ul style="list-style-type: none"> These patients have a low nutrition risk

NUTRIC, Nutrition Risk in Critically ill; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment.

TABLE 3 Nutrition Risk Screening 2002

Initial risk screening		Yes	No
1	Is BMI <20?	—	—
2	Has the patient lost weight within last 3 months?	—	—
3	Has the patient had a reduced dietary intake in the last week?	—	—
4	Is the patient severely ill? (e.g., in intensive therapy)	—	—
If the answer is "Yes" to any question, the screening in final screening is performed			
If the answer is "No" to all questions, the patient is rescreened at weekly intervals. If the patient is scheduled for a major operation, a preventive nutrition care plan is considered to avoid the associated risk status			
Final screening			
Impaired nutritional status		Severity of disease (increase in requirements)	
Absent (Score 0)	Normal nutritional status	Absent (Score 0)	Normal nutritional requirement
Mild (Score 1)	Weight loss >5% in 3 months or Food intake below 50–75% of normal requirement in preceding week	Mild (Score 1)	Hip fracture* Chronic patients in particular with complications: Cirrhosis*, COPD*, Chronic hemodialysis, diabetes, oncology
Moderate (Score 2)	Weight loss >5% in 2 months or BMI 18.5–20.5 + impaired general condition or Food intake 25–50% of normal requirement in preceding week	Moderate (Score 2)	Major abdominal surgery* Stroke* Severe pneumonia, hematologic malignancy
Severe (Score 3)	Weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 + impaired general condition or Food intake 0–25% of normal requirement in preceding week	Severe (Score 3)	Head injury Bone marrow transplantation Intensive care (APACHE >10)
Score + Score = Total score			
Age if ≥70 years: Add 1 to total score above = Age-adjusted score			
Score ≥3: The patient is nutritionally at risk and a nutrition care plan is initiated			
Score <3: Weekly rescreening of the patient. If the patient is scheduled for major operation, a preventive nutrition care plan is considered to avoid the associated risk status			

BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation.

Note: NRS-2002 is based on an interpretation of available randomized clinical trials. *Indicates that a trial directly supports the categorization of patients with that diagnosis.

A nutritional care plan is indicated in all patients who are:

- Severely undernourished (score = 3)
- Severely ill (score = 3)
- Moderately undernourished + mildly ill (score 2 + 1)
- Mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease score = 1: A patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

Score = 2: A patient confined to bed due to illness, e.g., following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.

Score = 3: A patient in intensive care with assisted ventilation, etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

patients in order to determine both the nutritional status and disease severity

Patients at "risk" are identified by:

- Nutritional Risk Score 2002 >3 and those at "high risk" with a score ≥5

- A NUTRIC score ≥5 (if interleukin-6 is not included, otherwise >6).

It was emphasized that nutrition assessment should include an evaluation of comorbid conditions, function of the gastrointestinal (GI) tract, and risk of aspiration. Use of

traditional, serum protein markers (albumin, prealbumin, transferrin and retinol-binding protein) was discouraged, as they do not accurately represent nutrition status in the ICU setting but reflects the acute-phase response (increases in vascular permeability and reprioritization of hepatic protein synthesis). The use of indirect calorimetry (IC) was recommended as the best tool for determining energy requirement. Predictive energy calculation tools (Harris-Benedict, Ireton Jones, Penn state) or simple weight based equations (25–30 kcal/kg/day) can be used.

Initiating Enteral Nutrition

Early enteral nutrition (EN) was emphasized to be initiated within 24–48 hours in patient who is unable to take orally. The specific reasons for providing EN are to maintain gut integrity, modulate systemic immune response, and attenuate disease severity. Use of EN over parenteral nutrition (PN) was emphasized as the use of EN is associated with a reduction in infectious morbidity (generally, pneumonia and central line infections and abdominal abscess in trauma patients) and ICU LOS.

Gastrointestinal motility should be evaluated in the majority of patients when initiating EN, overt signs of contractility should not be required prior to initiation of EN. Reduced or absent bowel sounds may only reflect greater disease severity. In most patients, it is acceptable to initiate EN in the stomach, but it should be given lower in the GI tract in patients who are at high risk for aspiration or have intolerance to gastric EN.^{6,7} In hemodynamically unstable patients, EN should be withheld until the patient is stable. It may be started with caution during withdrawal of vasopressor support. Signs of intolerance [abdominal distention, increasing nasogastric (NG) output or gastric residual volume (GRV), decreased passage of stool and flatus, hypoactive bowel sounds, increasing metabolic acidosis, and/or base deficit] in patients on vasopressor therapy receiving EN could be indicative of gut ischemia, and EN should be held until symptoms stabilize.

Dosing of Enteral Nutrition

Patients who are at low nutrition risk and baseline normal nutritional status (e.g., NRS 2002 ≤ 3 or NUTRIC score ≤ 5) and cannot take orally do not require specialized nutrition therapy during the first week in the ICU. These low-risk patients should be reassessed daily, and if their disease severity, or expected LOS worsens, the risk/benefit ratio may favor initiation of EN therapy. Either trophic or full nutrition by EN is appropriate for patients with acute respiratory distress syndrome (ARDS) and those expected to have a duration of mechanical ventilation ≥ 72 hours.^{8,9} Trophic EN is defined as 10–20 kcal/h or up to 500 kcal/day. Sufficient protein should be provided in these patients. Protein requirements are in the range of 1.2–2.0 g/kg/day in burn or multitrauma patients.

Monitoring Tolerance and Adequacy of Enteral Nutrition

Daily monitoring for tolerance of EN should be done and inappropriate cessation of EN should be avoided. Nil by mouth during diagnostic tests or procedures should be minimized. Gastrointestinal intolerance is defined by vomiting, abdominal distention, discomfort, high NG output, high GRV, diarrhea, reduced passage of flatus and stool, or abnormal abdominal radiographs. Gastric residual volumes should not be used as part of routine care in patients receiving EN. If GRVs are still utilized, holding EN for GRVs < 500 mL in the absence of other signs of intolerance should be avoided. Use of GRVs leads to increased enteral access device clogging, inappropriate cessation of EN, and consumption of nursing time and may adversely affect outcome due to less EN volume delivery. If GRVs is eliminated, careful daily physical examinations, review of abdominal radiologic films, and evaluation of clinical risk factors for aspiration should be done. Enteral nutrition protocols should be initiated, and efforts to proactively reduce risk of aspiration pneumonia should be made. It was recommended that in patients at high risk for aspiration, the level of feeding should be diverted by postpyloric enteral access device placement.¹⁰

It was recommended that enteral feeding protocols and their proper implementation should be in place.^{11–13} Use of ICU- or nurse-driven protocols (defining EN infusion rate goals, specific orders for handling GRVs, frequency of flushes and conditions or problems under which EN may be adjusted or stopped) increase the overall percentage of energy-provided and volume-based feeding protocols targeting 24-hour or daily volumes instead of hourly rates increase the volume of nutrition delivery.

For high-risk patients or intolerant to bolus gastric EN, delivery of EN should be switched to continuous infusion. Prokinetic medications (metoclopramide or erythromycin), may be initiated in such patients.

In all intubated patients receiving EN, the head of the bed should be elevated 30–45° and chlorhexidine mouthwash twice a day should be used. Enteral nutrition should not be automatically interrupted for diarrhea, but rather that feeds to be continued while evaluating the etiology of diarrhea. Assessment of diarrhea should include an abdominal examination, quantification of stool, stool culture for *Clostridium difficile* (and/or toxin assay), serum electrolyte panel, and review of medications. One needs to distinguish infectious diarrhea from osmotic diarrhea.

Selection of Appropriate Enteral Formulations

A standard polymeric formula when initiating EN should be used. Specialty formulas should generally be avoided. A standard polymeric isotonic feed 1–1.5 kcal/mL formula is appropriate and is well tolerated. One exception is the use of an immunomodulating formula in the postoperative patient

in a SICU setting. It was suggested that immunomodulating enteral formulations [arginine with other agents, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), glutamine and nucleic acid) should not be used routinely in the medical ICU (MICU) and their use should be reserved for patients with TBI and perioperative patients in the SICU. There are conflicting data regarding the use of an enteral formulation characterized by an anti-inflammatory lipid profile [e.g., ω -3 fish oil (FO) and borage oil] and antioxidants in patients with ARDS and severe acute lung injury (ALI) and no recommendation was done.

A mixed fiber formula should not be used routinely prophylactically to promote bowel regularity or prevent diarrhea. Their use was suggested, if there was evidence of persistent diarrhea. It was suggested to avoid both soluble and insoluble fiber in patients at high risk for bowel ischemia or severe dysmotility. It was also suggested to consider use of small peptide formulations in the patient with persistent diarrhea, with suspected malabsorption or lack of response to fiber.

Adjunctive Therapy

A fermentable soluble fiber additive [e.g., fructooligosaccharides (FOSs) and inulin] should be considered for routine use in all hemodynamically stable patients on a standard enteral formulation. Ten to twenty grams of a fermentable soluble fiber supplement should be given in divided doses over 24 hours as adjunctive therapy, if there is evidence of diarrhea.

Soluble fiber shows a more consistent benefit for reducing diarrhea than commercial mixed fiber formulas. Fructooligosaccharides are indigestible carbohydrates fermented in the colon into short-chain fatty acids (SCFAs). Shortchain fatty acids (especially butyrate) provide nutrition for the colonocyte, increase colonic blood flow, and stimulate pancreatic secretions and have an impact on the gut microbiota and the gut barrier function. Prebiotics (e.g., FOS and inulin) stimulate the growth of *Bifidobacteria* and *Lactobacillus*, the "healthy" bacteria. Probiotics should be used only for select medical and surgical patient populations, e.g., liver transplantation, trauma, and pancreatectomy.

It was suggested that a combination of antioxidant vitamins and trace minerals should be provided to those patients who require specialized nutrition therapy. Antioxidant vitamins (including vitamins E and C—ascorbic acid) and trace minerals (including selenium, zinc, and copper) may improve patient outcome, especially in burns, trauma, and critical illness-requiring mechanical ventilation.

It was suggested that supplemental enteral glutamine should not be added to an EN regimen routinely in critically ill patients.¹⁴ While enteral glutamine exerts a trophic effect in maintaining gut integrity, its failure to generate a sufficient systemic antioxidant effect may partially explain the lack of outcome benefit.

When to use Parenteral Nutrition?

Guidelines suggest that in the patient at low nutrition risk (e.g., NRS 2002 ≤ 3 or NUTRIC score ≤ 5), PN be withheld over the first 7 days following ICU admission, if the patient cannot take orally and if early EN is not feasible. The risk/benefit ratio for use of PN in the ICU setting is much narrower than that for use of EN. Available evidence recommends withholding PN for 10–14 days, but the guidelines committee was concerned that no nutrition beyond 7 days would lead to deterioration of nutrition status and an adverse effect on clinical outcome.

It was suggested to initiate exclusive PN, when EN was not feasible, as soon as possible following ICU admission in the patient at high nutrition risk (e.g., NRS 2002 ≥ 5 or NUTRIC score ≥ 5) or severely malnourished. Supplemental PN after 7–10 days was recommended, in patients at either low- or high-nutrition risk, if they are unable to meet $>60\%$ of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this 7- to 10-day period in critically ill patients on some EN does not improve outcomes and may be detrimental to the patient.^{15,16} Published studies have not shown any outcome benefit of early PN and the optimal time to initiate supplemental PN in a patient receiving hypocaloric EN is not clear. In such situations, the addition of supplemental PN should be considered, on a case-by-case basis.

Maximise Efficacy of Parenteral Nutrition

It was suggested that the use of protocols and nutrition support teams reduce risk of PN. It was suggested that hypocaloric PN dosing (≤ 20 kcal/kg/day or 80% of estimated energy needs) with adequate protein (≥ 1.2 g protein/kg/day) should be considered initially over the first week of hospitalization in the ICU, in patients with high risk or severely malnourished. This strategy may optimize the efficacy of PN in the early phases of critical illness by reducing the potential for hyperglycemia and insulin resistance use of soybean oil (SO)-based intravenous fat emulsions (IVFEs) should be avoided during the first week following initiation of PN. If there is concern for essential fatty acid deficiency, a maximum of 100 g/week (often divided into two doses per week) may be given.

Alternative IVFEs [safety and efficacy of a new parenteral lipid emulsion (SMOF)—soybean oil, medium-chain triglycerides (MCTs), olive oil (OO), and FO emulsion], MCT, OO, and FO should be considered for PN.

A target blood glucose range of 140 or 150–180 mg/dL for the general ICU population was recommended.^{17,18} It was recommended that parenteral glutamine supplementation should not be used routinely in the critical care setting.¹⁹

It was suggested that as tolerance to EN improves, the amount of PN energy should be reduced and finally discontinued when the patient is receiving $>60\%$ of target

energy requirements from EN. Because of the marked benefits of EN, repeated efforts should be made to transition the patient from PN to enteral therapy. To avoid the complications associated with overfeeding, the amount of energy delivered by the parenteral route should be reduced to compensate for the increase in the energy being delivered enterally.

DISEASE-SPECIFIC RECOMMENDATIONS

Pulmonary Failure

It was suggested not to use high-fat/low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce carbon dioxide production in ICU patients with acute respiratory failure. Fluid-restricted energy-dense EN formulations for patients with acute respiratory failure (especially, if in a state of volume overload) were recommended. Serum phosphate concentrations should be monitored closely and replaced appropriately when needed. Phosphate is essential for the synthesis of adenosine triphosphate and 2,3-diphosphoglycerate, both of which are critical for normal diaphragmatic contractility and optimal pulmonary function. Hypophosphatemia may represent an occult cause of respiratory muscle weakness and failure to wean from the ventilator.

Renal Failure

It was suggested that ICU patients with acute renal failure or acute kidney injury be placed on a standard enteral formulation and that standard ICU recommendations for protein (1.2–2 g/kg actual body weight per day) and energy (25–30 kcal/kg/day) provision should be followed. If significant electrolyte abnormalities develop, a specialty formulation designed for renal failure (with appropriate electrolyte profile) may be considered.

Patients on hemodialysis or continuous renal replacement therapy should receive increased protein, up to a maximum of 2.5 g/kg/day. Protein should not be restricted in patients with renal insufficiency as a means to avoid or delay initiating dialysis therapy.

Hepatic Failure

It was suggested that a dry weight or usual weight be used instead of actual weight in predictive equations to determine energy and protein in patients with cirrhosis and hepatic failure, due to complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia. Protein restriction should be avoided, EN should be used preferentially with standard enteral formulations be used in patients with acute and chronic liver disease. There is no evidence of further benefit of branched-

chain amino acid formulations on coma grade in the ICU patient with encephalopathy who is already receiving first-line therapy with luminal-acting antibiotics and lactulose.

Acute Pancreatitis

Evaluate disease severity to direct nutrition therapy. Since disease severity may change quickly, it was suggested that frequent reassessment of feeding tolerance and need for specialized nutrition therapy should be done. In mild acute pancreatitis advance to an oral diet as tolerated. If an unexpected complication develops or there is failure to advance to oral diet within 7 days, then specialized nutrition therapy should be considered.

It was suggested that patients with moderate-to-severe acute pancreatitis should have a naso-/oral-enteric tube placed and EN started at a trophic rate and advanced within 24–48 hours of admission. It was suggested to use a standard polymeric formula to initiate EN in the patient with severe acute pancreatitis. Data is insufficient to recommend placing a patient with severe acute pancreatitis on an immune-enhancing formulation.

It was suggested to use EN over PN by either the gastric or jejunal route in patients with severe acute pancreatitis as there is no difference in tolerance or clinical outcomes between these. Consider use of probiotics. Use of PN should be considered after 1 week from the onset of the pancreatitis episode.

Surgical Subsets

Trauma

Early enteral feeding with a high-protein polymeric diet should be initiated in the immediate post-trauma period (within 24–48 h of injury) once the patient is hemodynamically stable. Immunomodulating formulations containing arginine and FO should be considered in patients with severe trauma.

Traumatic Brain Injury

Early enteral feeding should be initiated in the immediate post-trauma period (within 24–48 hours of injury) once the patient is hemodynamically stable, either arginine-containing immunomodulating formulations or EPA/DHA supplement with standard enteral formula in patients with TBI should be considered.

Open Abdomen

Early EN (24–48 h postinjury) in the absence of a bowel injury. It is provided an additional 15–30 g of protein per liter of exudate lost.

Burns

Provide EN early within 4–6 hours of injury. Parenteral nutrition should be reserved for those burn patients for whom EN is not feasible or not tolerated. Protein in the range of 1.5 to 2 g/kg/day should be provided.

Sepsis

Start EN therapy within 24–48 hours of making the diagnosis of severe sepsis/septic shock as soon as resuscitation is complete and the patient is hemodynamically stable. It was suggested to not use exclusive PN or supplemental PN in conjunction with EN early in the acute phase of severe sepsis or septic shock, regardless of patients' degree of nutrition risk. Provide trophic feeding (defined as 10–20 kcal/h or up to 500 kcal/day) for the initial phase of sepsis, advancing as tolerated after 24–48 hours to >80% of target energy goal over the first week. Delivery of 1.2–2 g protein/kg/day is suggested. Immunomodulating formulas should not be used routinely in patients with severe sepsis.^{20,21}

Postoperative Major Surgery

Enteral nutrition should be provided when feasible in the postoperative period within 24 hours of surgery, as it results in better outcomes than PN.

Routine use of an immunomodulating formula (containing both arginine and FO) may be considered. Enteral feeding should be considered even in difficult postoperative situations such as prolonged ileus, intestinal anastomosis, open abdomen and need of vasopressors for hemodynamic support. For the patient who has undergone major upper GI surgery and EN is not feasible, PN should be initiated (only if the duration of therapy is anticipated to be ≥ 7 days). Unless the patient is at high-nutrition risk, PN should not be started in the immediate postoperative period but should be delayed for 5–7 days. Patients should be allowed solid food as tolerated and that clear liquids are not required as the first meal.

Chronically Ill Patient

It was suggested that chronically critically ill patients (defined as those with persistent organ dysfunction requiring ICU LOS >21 days) be managed with aggressive high-protein EN therapy and when feasible, that a resistance exercise program be used.

Obesity in Critical Illness

Early EN should start within 24–48 hours of ICU admission for obese patients who cannot take orally. It was suggested that nutrition assessment of the obese ICU patient focus on biomarkers of metabolic syndrome, an evaluation of

comorbidities and a determination of level of inflammation. It was also suggested that nutrition assessment of the obese ICU patient focus on evidence of central adiposity, metabolic syndrome, sarcopenia, body mass index (BMI) >40, systemic inflammatory response syndrome (SIRS) or other comorbidities that correlate with higher obesity-related risk for cardiovascular disease and mortality.

High-protein hypocaloric feeding should be implemented in the care of obese ICU patients to preserve lean body mass, mobilize adipose stores and minimize the metabolic complications of overfeeding. It was suggested that, for all classes of obesity, the goal of the EN regimen should not exceed 65–70% of target energy requirements as measured by IC. If IC is unavailable, weight-based equation 11–14 kcal/kg actual body weight per day for patients with BMI in the range of 30 to 50 and 22 to 25 kcal/kg ideal body weight per day for patients with BMI >50 may be used. Protein should be provided in a range from 2.0 g/kg ideal body weight per day for patients with BMI of 30–40 up to 2.5 g/kg ideal body weight per day for patients with BMI >40.

An enteral formula with low-caloric density and a reduced nonprotein calorie to nitrogen ratio be used in the adult obese ICU patient. While an exaggerated immune response in obese patients implicates potential benefit from immunomodulating formulas, lack of outcome data precluded any recommendation. Additional monitoring to assess worsening of hyperglycemia, hyperlipidemia, hypercapnia, fluid overload, and hepatic fat accumulation in the obese critically ill patient receiving EN should be done.

It is suggested that the obese ICU patient with a history of bariatric surgery receive supplemental thiamine prior to initiating dextrose-containing intravenous fluids or nutrition therapy. In addition, evaluation for and treatment of micronutrient deficiencies, such as calcium, thiamin, vitamin B12, fat-soluble vitamins (A, D, E, and K) and folate, along with the trace minerals iron, selenium, zinc, and copper should be considered in these patients.

Nutrition Therapy for End-of-life Situations

It was suggested that artificial nutrition and hydration (ANH) was not obligatory in cases of futile care or end-of-life situations. The decision to provide ANH should be based on evidence, best practices, clinical experience, and judgment; effective communication with the patient, family, and/or authorized surrogate decision maker; and respect for patient autonomy and dignity.

CONCLUSION

The 2016 ASPEN-SCCM guidelines include several new/modified recommendations (Box 1):

- Early assessment of patients admitted to the ICU for nutrition risk using nutrition-scoring systems

Box 1: Nutrition bundle statements¹

- Assess patients on admission to the intensive care unit (ICU) for nutrition risk, and calculate both energy and protein requirements to determine goals of nutrition therapy
 - Initiate enteral nutrition (EN) within 24–48 h following the onset of critical illness and admission to the ICU, and increase to goals over the first week of ICU stay
 - Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding (use prokinetic agent, continuous infusion, chlorhexidine mouthwash, elevate the head of bed, and divert level of feeding in the gastrointestinal tract)
 - Implement enteral feeding protocols with institution-specific strategies to promote delivery of EN
 - Do not use gastric residual volumes as part of routine care to monitor ICU patients receiving EN
 - Start parenteral nutrition early when EN is not feasible or sufficient in high-risk or poorly nourished patients
- Initiation of EN within 24/48 hours following the onset of critical illness and admission to the ICU
 - Steps to reduce risk of aspiration and improve tolerance of enteral feeding
 - Elimination of the use of GRVs as part of routine care for ICU patients
 - Initiation of PN early, if EN is not feasible
 - There was grade A and grade B recommendation for immunomodulatory therapy in surgical and medical patients in 2009. The 2016 guidelines recommend that immunomodulatory therapy should not be used routinely in MICU and use should be reserved for patients with TBI and perioperative patients in SICU
 - A major change is in the recommendation for anti-inflammatory lipids and antioxidants in ARDS and severe ALI. In 2009, it was grade A recommendation to use this therapy, but 2016 guidelines state that no recommendations can be made regarding their use
 - There is a change in recommendation for antioxidants vitamins and trace minerals therapy. In 2009, it was grade B recommended for all critically ill patients, whereas in 2016, it is recommended in safe doses to patients requiring specialized nutrition therapy and may improve outcome in burns, trauma and critical illness requiring mechanical ventilation
 - The target blood sugar levels have been increased from 80–110 mg/dL in 2009 guidelines to 140–180 mg/dL in 2016 recommendations.

REFERENCES

1. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2016;40:159–211.

2. Guyatt GH, Oxman AD, Vist G, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924–6.
3. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2009;33:277–316.
4. Kondrup J, Rasmussen HH, Hamberg O, et al. Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr.* 2003;22:321–36.
5. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care.* 2011;15:R268.
6. Davies AR, Morrison SS, Bailey MJ, et al. A multicenter, randomized controlled trial comparing early nasogastric feeding with nasogastric nutrition in critical illness. *Crit Care Med.* 2012;40:2342–8*.
7. Kearns PJ, Chin D, Mueller L, Wallace K, et al. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. *Crit Care Med.* 2000;28(6):1742–6*.
8. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA.* 2012;307:795–803*.
9. Rice TW, Mogan S, Hays MA, et al. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med.* 2011;39:967–974*.
10. Heyland DK, Drovèr JW, MacDonald S, et al. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. *Crit Care Med.* 2001;29:1495–501*.
11. Heyland DK, Murch L, Cahill N, et al. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. *Crit Care Med.* 2013;41:2743–53*.
12. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA.* 2008;300:2731–41*.
13. Barr J, Hecht M, Flavin KE, et al. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest.* 2004;125:1446–57*.
14. Hall JC, Dobb G, Hall J, de Sousa R, et al. A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med.* 2003;29:1710–6*.
15. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* 2011;365:506–17*.
16. Kutsogiannis J, Alberda C, Gramlich L, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. *Crit Care Med.* 2011;39:2691–9*.
17. Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med.* 2012;40:3251–76*.
18. NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su Y, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283–97*.
19. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med.* 2013;368:1489–97*.
20. Galban C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med.* 2000;28:643–8*.
21. Drovèr JW, Dhaliwal R, Weitzel L, et al. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. *J Am Coll Surg.* 2011;212:385–99, 399.e1*.

Fungal Sepsis in Acute Necrotizing Pancreatitis

Ashit V Hegde

INTRODUCTION

Fungal infections are an important contributor to mortality and morbidity in critically ill patients. *Candida* is the fourth or fifth most common pathogen isolated from blood cultures in intensive care units (ICUs) across the world.^{1,2} Morphologically, acute pancreatitis is classified into:

- Interstitial edematous pancreatitis
- Necrotizing pancreatitis (characterized by absence of enhancement following contrast administration).

The severity of pancreatitis is determined by the presence or absence of organ failure or local complications and by the duration of organ failure.³

PATHOGENESIS OF FUNGAL INFECTIONS⁴

The first step in the development of invasive fungal infections (IFIs) usually is the colonization of a patient's skin or mucous membrane by *Candida*. A breach in the integumentary barriers associated with some degree of immune suppression may then cause these *Candida* to become pathogenic. Factors, which promote colonization (broad spectrum antibiotics and high glucose levels), which cause a breach of the natural barriers (central lines and mucositis) and which cause immunosuppression (steroids, sepsis, and immunosuppressive drugs) make patients more vulnerable to IFI. The single most important risk factor for IFI, however, is duration of stay in ICU. A recent study⁵ seemed to suggest that IFIs are seen earlier in Indian ICUs as compared to western ICUs (8 days vs. 12 days).

SEVERE PANCREATITIS AND INVASIVE FUNGAL INFECTION

Patients with acute necrotizing pancreatitis have many of these risk factors. It is, therefore, not surprising that they are prone to fungal sepsis. However, sepsis is not a cause of early mortality in patients with severe acute pancreatitis. Early

mortality is usually due to a severe systemic inflammatory response syndrome. Both, under- and over-resuscitation (causing the abdominal compartment syndrome) may contribute to early mortality.^{6,7} Delayed mortality is most often due to infection. The most common source of sepsis in this group of patients is infected pancreatic necrosis. Infected necrosis occurs in approximately 40–70% of patients with necrotic pancreatitis.⁸ Gram-negative organisms are the most common causes of infected pancreatic necrosis. The first reports of pancreatic fungal infections (PFI) were published in the 1980s⁹ and are now being increasingly recognized. These patients are also at risk of developing bloodstream infections caused by *Candida*. It is thought that microorganisms reach the necrotic pancreas via the inflamed gut. Earlier studies seemed to suggest that prophylactic antibiotics (especially, carbapenems) might reduce the incidence of infected pancreatic necrosis. Subsequent studies have failed to confirm this role of prophylactic antibiotics¹⁰ and most guidelines no longer recommend prophylactic antibiotics in the management of severe pancreatitis. Unfortunately, in actual practice, however, many patients continue to receive prophylactic antibiotics. Early enteral feeding might also prevent gut atrophy and translocation of microorganisms. It is, therefore, recommended that patients with pancreatitis be fed enterally as early as possible.¹¹ Again enteral feeding is delayed quite often in many patients and many such patients receive total parenteral nutrition (TPN) via a central line. Thus, inappropriate early management of severe acute pancreatitis is an important factor (but probably not the only factor) in the development of fungal sepsis.

CLASSIFICATION OF PANCREATIC FUNGAL INFECTIONS¹²

Fungal infections of the pancreas are classified as primary or secondary. A Primary fungal infection indicates that the positive-fungal culture was obtained before any intervention was done. If the positive culture is obtained following

any intervention [endoscopic retrograde cholangiopancreatography (ERCP), surgery, and radiologic drainage], it is classified as secondary fungal pancreatitis.

Patients with primary *Candida* infection, quite often have coexisting Gram-positive infections while patients with secondary infection are more prone to Gram-negative infections. Secondary fungal pancreatic infection is associated with a poorer prognosis.

MICROBIOLOGY

There has been an increase in the isolation of non-*albicans* *Candida* both from blood cultures and from cultures of the necrotic pancreatic tissue. In the western ICUs, *Candida krusei* and *Candida glabrata* are frequently isolated.¹³ In India, *Candida tropicalis* is the most frequently isolated non-*Candida albicans* organism. In many Indian ICUs, *Candida tropicalis* is even more frequent than *Candida albicans*.

In a study conducted in Indian intensive care,¹⁴ 40% of the *Candida* isolated from the pancreas were *Candida tropicalis*. *Candida krusei* and *Candida glabrata* are relatively rare in most general medical and general surgical Indian ICU's. This might have implications for therapy because most of the non-*albicans* species isolated in India remain fluconazole sensitive.

CLINICAL FEATURES

There are no clinical features unique to fungal infection in patients with pancreatitis.

Infected necrosis usually occurs after 14 days and manifests with fever, abdominal pain, and worsening of the patient's condition after initial stabilization.

Pancreatic fungal infection should be thought of in patients with suspected infected necrosis especially, if they do not respond to broad spectrum antibiotics or if they have one or more of the risk factors for fungal pancreatitis (broad spectrum antibiotics, TPN, central lines, ERCP, uncontrolled sugars, *Candida* colonization).

DIAGNOSIS

Infected necrosis, once suspected, is confirmed by the presence of gas in the retroperitoneum or by a computed tomography or ultrasonography-guided fine needle aspiration cytology of the necrotic tissue.^{15,16} To conclusively diagnose fungal pancreatitis, *Candida* must grow in the culture of the aspirate or must be seen on histopathology. Blood cultures may be sent but are negative >50% of the time.

The role of nonculture-based tests (biomarkers and polymerase chain reaction) has not yet been established.

Definite diagnosis may not always be possible or may be delayed. Physicians quite often have to, therefore, resort to empiric therapy in sick patients with one or more risk factors for fungal infections.

TREATMENT

Traditionally, liposomal amphotericin has been recommended as the treatment of choice for fungal pancreatitis. Fluconazole has good penetration into the pancreatic bed¹⁷ and might be a reasonable substitute especially in patients without prior azole exposure and in units where the incidence of azole-resistant *Candida* is low. Fluconazole needs to be dosed properly (800 mg on day 1 followed by at least 400 mg daily). There is very little knowledge of the penetration of the echinocandins into pancreatic tissue. There is hardly any data on the use of echinocandins for the treatment of PFI. Until we have more data, these drugs cannot be recommended for the treatment of PFI. Echinocandins may, however, be used to treat patients with candidemia without pancreatic infection (especially, those who are hemodynamically unstable or have had prior exposure to azoles). An attempt to de-escalate from liposomal amphotericin or echinocandins to fluconazole must be made once the patient is stable and culture results are back.

SOURCE CONTROL

The patients will also need debridement or drainage of the infected tissue. Any attempt at surgical debridement should be delayed by a few weeks, if possible, as per the current recommendations.¹⁸ Surgical planes are more clearly defined when surgery is delayed and the morbidity associated with surgery is clearly decreased. However, minimally invasive techniques to drain the necrotic tissue (under radiologic guidance) may be attempted earlier.

PROPHYLAXIS

Prophylactic administration of fluconazole to patients with pancreatitis who have received antibiotics has been shown to decrease the incidence of PFI in a few studies.¹⁹ However, given the risk of selecting for resistant fungi, it probably makes more sense to avoid antibiotics and antifungals, feed enterally early, and to avoid TPN.

PROGNOSIS

Some studies have shown increased mortality with PFI²⁰ whereas other studies (usually performed in specialized tertiary care centers)²¹ have not shown any increase in mortality. Early institution of antifungal therapy seems to decrease mortality. But most studies suggest that PFI increase morbidity, utilization of ICU resources, and cost.

CONCLUSION

Pancreatic fungal infections are being increasingly recognized and definitely contribute to morbidity if not

mortality. In India, most infections are caused by azole-sensitive *Candida*. Fine needle aspiration cytology of the necrotic tissue is the only way to confirm PFI.

Most patients with risk factors may need empiric therapy. Fluconazole may be used for all but the most sick patients in whom liposomal amphotericin may be preferred.

Appropriate early management (avoid antibiotics, feed enterally early, and avoid TPN) is probably better than drug prophylaxis at preventing PFI.

REFERENCES

1. Wisplinghoff H, Bischoff T, Tallent SM, et al. Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) study. *Clin Infect Dis*. 2004;39:309-17.
2. Parameswaran R, Sherchan JB, Varma DM, et al. Intravascular catheter-related infections in an Indian tertiary care hospital. *J Infect Dev Ctries*. 2011;5:452-8.
3. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102-11.
4. Garcia-Vidal C, Viasus D, Carratalà J. Pathogenesis of invasive fungal infections. *Curr Opin Infect Dis*. 2013;26:270-6.
5. Chakrabarti A, Sood P, Rudramurthy SM, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. *Intensive Care Med*. 2015;41:285-95.
6. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatol*. 2009;9:770-6.
7. de-Madaria E, Soler-Sala G, Sánchez-Paya J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. *Am J Gastroenterol*. 2011;106:1843-50.
8. Beger HG, Rau B, Mayer J, et al. Natural course of acute pancreatitis. *World J Surg*. 1997;21:130-5.
9. Richter JM, Jacoby GA, Schapiro RH, et al. Pancreatic abscess due to *Candida albicans*. *Ann Intern Med*. 1982;97:221-2.
10. Jiang K, Huang W, Yang XN, et al. Present and future of prophylactic antibiotics for severe acute pancreatitis. *World J Gastroenterol*. 2012;18:279-84.
11. Yi F, Ge L, Zhao J, Lei Y, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. *Intem Med*. 2012;51:523-30.
12. De Waele J, Vogelaers D, Decruyenaere J, et al. Infectious complications of acute pancreatitis. *Acta Clin Belg*. 2004;59:90-6.
13. Grewe M, Tsiotos GG, deLeon EL, et al. Fungal infection in acute necrotizing pancreatitis. *J Am Coll Surg*. 1999;188:408-14.
14. Chakrabarti A, Rao P, Tarai B, et al. *Candida* in acute pancreatitis. *Surg Today*. 2007;37:207-11.
15. Uhl W, Warshaw A, Imrie C, et al. IAP Guidelines for the Surgical Management of Acute Pancreatitis. *Pancreatol*. 2002;2:565-73.
16. Banks PA, Gerzof SG, Langevin RE, et al. CT-guided aspiration of suspected pancreatic infection: bacteriology and clinical outcome. *Int J Pancreatol*. 1995;18:265-70.
17. Shrikhande S, Friess H, Issenegger C, et al. Fluconazole penetration into pancreas. *Antimicrob Agents Chemother*. 2000;44:2569-71.
18. Mouli VP, Vishnubhatla S, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology*. 2013;144:333-40.
19. De Waele JJ, Vogelaers D, Blot S, et al. Fungal infections in patients with severe acute pancreatitis and the use of prophylactic therapy. *Clin Infect Dis*. 2003;37:208-13.
20. Connor S, Alexakis N, Neal T, Raraty M, et al. Fungal infection but not type of bacterial infection is associated with a high mortality in primary and secondary infected pancreatic necrosis. *Dig Surg*. 2004;21:297-304.
21. Vege SS, Gardner TB, Chari ST, et al. Outcomes of intra-abdominal fungal vs. bacterial infections in severe acute pancreatitis. *Am J Gastroenterol*. 2009;104:2065-70.

Acute Colonic Pseudo-obstruction

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INTRODUCTION

Acute colonic pseudo-obstruction (ACPO) is also known as Ogilvie syndrome. Sir William Heneage Ogilvie in the year 1948 described two cases of colonic dilatation without mechanical obstruction. Both patients had retroperitoneal tumors invading the splanchnic plexus leading to destruction of splanchnic nerves, semilunar ganglia, and the celiac plexus, hence the parasympathetic innervations in the colon working was unopposed.¹ The term "pseudo-obstruction" was proposed by Dudley^{2,3} and the term "acute colonic pseudo-obstruction" appeared in the literature in the year 1982 when Nanni et al.⁴ used it for acute nonmechanical obstruction of large gut.

The acronym ACPO was used by Rex in his article in the year 1997.⁵ Presently, the term "acute colonic pseudo-obstruction" is more prevalent in the literature to describe this phenomenon.⁶

Acute colonic pseudo-obstruction is characterized by massive colonic dilatation with symptoms and signs of colonic obstruction without mechanical blockade.⁷ It generally occurs in critically ill patients with sepsis, recent surgeries, electrolyte abnormalities, and trauma. The actual mechanism of this disorder is unknown, but it is believed that some abnormality affecting the autonomic nervous system (ANS) might be involved. It is more common in male particularly who are older than 60 years.

EPIDEMIOLOGY

A review of 400 cases of Ogilvie syndrome by Vanek et al.⁸ in the year 1986 revealed that males presented more frequently than females, with an average age of 59.9 years for males and 56.5 years for females.⁸ Of all the cases, 94.5% had an association with medical or surgical condition like obstetric, gynecologic, or pelvic operation (19%); post-trauma orthopedics procedure (18%); infection (10%); cardiac event (10%), and neurologic event (9%).⁸ Other factors that

Box 1: Associations underlying acute colonic pseudo-obstruction

- Medications: Narcotics, anticholinergics, laxative abuse, benzodiazepines, calcium channel blockers, interleukin, amphetamine overdose, cytotoxic drugs, antiparkinsonian agents
- Medical
 - Neurologic: Dementia, Parkinson's disease, spinal cord disease
 - Metabolic: Hypokalemia, hyponatremia, hypocalcemia, hypercalcemia, diabetes, hypothyroidism
 - Cardiopulmonary: Mechanical ventilation, myocardial infarction, pneumonia, congestive heart failure, chronic obstructive pulmonary disease
 - Oncologic: Small cell lung cancer, multiple myeloma, acute myeloid leukemia, disseminated cancer, pelvic irradiation, retroperitoneal invasion of lumbar sympathetic nervous system
 - Infectious: Sepsis, Cytomegalovirus
 - Miscellaneous: Organ failure, alcoholism
- Surgical
 - Obstetric: Normal pregnancy, normal delivery, cesarean section, hysterectomy
 - Urologic: Ethanol ablation of renal cancer
 - Inflammation: Appendicitis, cholecystitis, pancreatitis, abscess
 - Organ transplantation: Liver, kidney, heart, lung
 - Trauma and orthopedic: Pelvic trauma, pelvic, hip fracture, pelvic, hip surgery, spine surgery, burns
 - Others: Gastrointestinal bleeding, retroperitoneal hematoma, mesenteric thrombosis, craniotomy, aortic aneurysms

contributed to the development of ACPO are electrolyte disturbances and narcotic use^{8,9} (Box 1).

ETIOLOGY AND PATHOPHYSIOLOGY

The pathogenesis of ACPO remains unknown but the most accepted theory is the imbalance in autonomic output to the colon produced by variety of factors leading to excessive parasympathetic suppression or sympathetic stimulation.⁷

The initial theory was an imbalance in activity of ANS with parasympathetic overactivity leading to dilatation of colon.¹ However, current evidence favors a relatively increased sympathetic tone and/or decreased parasympathetic tone leading to a functionally obstructing distal colon and a relaxed proximal colon.¹⁰ Enteric nerves contain a variety of neurotransmitters responsible for smooth muscle contraction and relaxation. Acetylcholine, neurokinin A, and substance P are major stimulatory neurotransmitters; whereas vasoactive intestinal polypeptide and nitric oxide are the inhibitory neurotransmitters.

Another theory suggests the interstitial cells of Cajal (ICC), present along the gastrointestinal (GI) tract in close association with smooth muscle cells, are elements of enteric nervous system. It is believed as the source of the spontaneous slow waves of gut musculature (pacemaker cells).¹¹ In one study performed by Jain et al., ICC were found to be absent in patients with chronic intestinal pseudo-obstruction.¹² Cytokines have also been found to alter the intestinal motility in an inflammatory state.¹³ The proven effectiveness of neostigmine in colonic pseudo-obstruction supports the validity of the theory suggested by Ogilvie of imbalance activity of ANS. With the progress in understanding of intestinal motility, ACPO has become an open avenue for novel therapeutic targets.

CLINICAL CHARACTERISTICS

Acute colonic pseudo-obstruction can have variable clinical presentation. The most common symptoms are abdominal distension, pain, nausea, vomiting, lack of gas passage, and constipation. About 40% of the patient with ACPO reports continued passage of flatus despite clinical evidence of obstruction.⁸ On clinical examination of the abdomen, tympanic and bowel sounds are typically present. The presence of marked abdominal tenderness, fever, and leukocytosis can be present as additional clinical findings. However, these findings are neither specific nor very sensitive towards definitive diagnosis. These patients also have respiratory compromise due to diaphragmatic compression. The above features are typical of large bowel obstruction which is commonly seen in patients with ACPO. A high index of suspicion with preexisting risk factors is necessary to make the clinical diagnosis. Many times, if left unrecognized or unaddressed, it can lead to perforation if the colonic diameter exceeds the threshold diameter of 9 cm.¹⁴ It becomes a serious concern when the diameter exceeds 12 cm. About 1–3% of the patients of ACPO develop perforation.^{8,15} Several studies indicate that perforation is rare with cecal diameter less than 12 cm. However, when the diameter exceeds 14 cm, perforation occurs in up to 23% of the patients.^{8,16} Perforation is associated with a mortality rate of 50–70%.^{8,15}

An increase in intramural pressure leads to ischemia with longitudinal splitting of the serosa and tenia which leads to herniation of the mucosa. The cecum is more susceptible

to distension induced ischemia and perforation as it is the thinnest wall area of colon.^{8,10,17} Once pressure inside the cecum exceeds that of superior mesenteric artery, pain and ischemia can occur. Signs of systemic toxicity do not appear until the catastrophic complications have occurred. Neuroischemia develops before perforation. Both ischemia and perforation give rise to high mortality in these patients. In a study by Vanek et al., the mortality increased from 26 to 44% in cases with perforated and ischemic bowel.⁸ Advanced age and delayed intervention are additional risk factors for increased mortality.⁸ Duration of distension also has a direct correlation with perforation. If the distension persists for more than 6 days, it carries a high risk for perforation.¹⁸

Exclusion of common causes of large bowel ileus, such as hypokalemia, hypocalcemia, hypomagnesemia, etc., early in the evaluation is important for clinical diagnosis and intervention. It is sometimes difficult to distinguish between perforation or ischemia and those with uncomplicated distension. Early use of diagnostic studies is helpful to avoid such kind of confusion.

DIAGNOSIS

High degree of suspicion and exclusion of other causes of mechanical obstruction of colon should be the first step towards the diagnosis of ACPO. The clinical presentation of ACPO and other causes of mechanical obstruction are nearly same. Hence, imaging method for diagnosis and differentiation is required. Plain radiograph can be a very good diagnostic tool for perforation. Serial films can be used to monitor the measurement of colonic dilatation. However, the distinction between mechanical and functional obstruction cannot be made with plain radiography alone. A contrast enema with computed tomography (CT) scan can be used as a useful diagnostic motility. It has got sensitivity and specificity of 80% and 100%, respectively, in the diagnosis of large bowel obstruction.¹⁹ A water soluble contrast is preferred because a small risk of extravasations of barium and more importantly, the potential therapeutic effect of water soluble contrast leading to decompression of the colon.²⁰ Excess contrast use should be avoided. It can be applied without bowel preparation.

Contrast retention may be difficult in elderly, frail, and critically ill patients. Exacerbation of dehydration and electrolyte imbalance can be a problem with hypotonic contrast solution.²¹ In a retrospective analysis done by Jacob et al., reveals an increasing trend towards the use of CT scan for the diagnosis of large bowel obstruction as compared to contrast enema.²² It is observed that CT scan has largely replaced the contrast enema for the diagnosis of large bowel obstruction.²² It is less problematic and requires intravenous contrast and a supine position of the patient. Moreover, images can be acquired quickly in a single breath-holding time. The sensitivity and specificity of CT scan is 96% and 93%, respectively, for the diagnosis of large bowel obstruction.¹⁹

Proximal colonic dilatation with an intermediate transitional zone at or adjacent to the splenic flexure is the common CT scan finding in ACPO patients. A CT scan can also diagnose complications including bowel ischemia, perforation, and condition of pericolic strictures.²¹

Distal mechanical colonic obstruction can be investigated with rectal examination, careful colonoscopy, CT scan (with intravenous, oral, or rectal contrast),²¹ or water soluble contrast enema. Colonoscopy can be diagnostic and therapeutic, but is often contraindicated when ischemia and perforation is suspected and can be challenging when performed in unprepared bowel and insufflation is required.²³

MANAGEMENT

Conservative Management

Early recognition is important in the management of ACPO. Close clinical monitoring in the form of physical examination (abdominal girth), abdominal radiographs, and laboratory studies every 12–24 hours, continuous bowel rest, nasogastric tube decompression, and rectal tube placement are a part of initial conservative management. Aggressive fluid and electrolyte resuscitation and antibiotics in case of suspected infection should be started. Investigation for contributing etiology, like hypothyroidism, diabetes mellitus, and other metabolic disorders, should be taken care of. Narcotics along with other offending medication should be stopped. Osmotic laxatives should be avoided in view of their increased tendency towards gas formation.²⁴ If possible, prone position with hip elevated on pillow or the knee-chest position with hips held high often helps in evacuation of flatus. These positions should be alternated with right and left lateral decubitus position regularly or every hourly when feasible.²⁵ In general, conservative therapy should be employed for 48–72 hours unless the patient demonstrates clinical deterioration.²⁴ Wegener et al. reviewed 1,027 case reports of ACPO and found that 70% of the patient responded to supportive management alone with a complication rate of 6% and mortality approximately 10%. The usual duration of response to these measures is 3–5 days.²⁶ In another study by Delgado-Aros et al., successful resolution is achieved in 83–96% patients within 2–6 days of conservative therapy.²⁷ It is important to note that if at any point during treatment, the patient condition deteriorates, investigation for ischemia and perforation should be undertaken immediately. Patients, who fail to improve after all conservative therapies mentioned above, should be considered for pharmacological therapy (Fig. 1).

Pharmacological Management (Table 1)

In one review published in 1982, it was advised against the use of pharmacological agents citing increased perforation

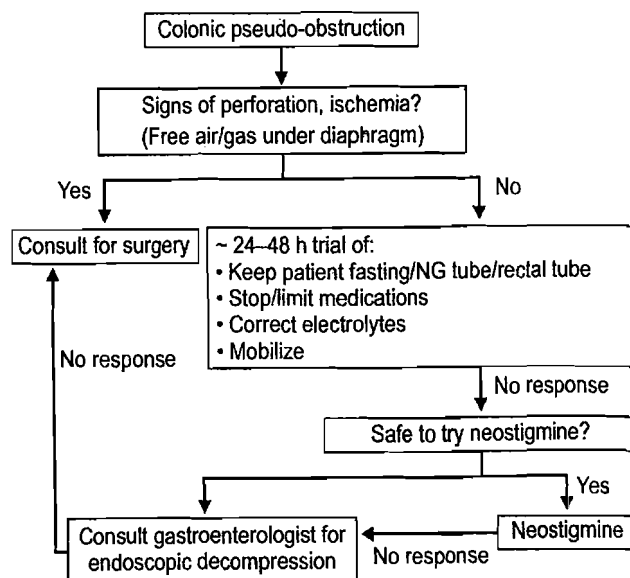


FIG. 1: Management of acute colonic pseudo-obstruction

TABLE 1 Pharmacologic management of acute colonic pseudo-obstruction

First line therapy	Neostigmine 2 or 2.5 mg IV bolus over 3–5 min Repeat dose up to 3 times if no response in 3 h
Salvage therapy	Neostigmine 0.4–0.8 mg/h infusion for 24 h or Pyridostigmine 10–30 mg orally two times a day
Adjunct to prevent relapse	29.5 g of polyethylene glycol in 500 mL of water orally in two doses
Opioid related ACPO	Naloxone – 0.4–2.0 mg Intravenous injection every other day to every day
Historical drugs	Erythromycin, metoclopramide, cisapride

ACPO, acute colonic pseudo-obstruction; IV, intravenous.

risk with inducing colonic contraction.⁴ There are number of case reports which were published in due course with erythromycin,²⁸ metoclopramide,²⁹ and cisapride³⁰ mentioning a beneficial effect as prokinetics in ACPO, but none of them revealed a consistent response in acute setting. A 40% success rate was reported with erythromycin by Emmanuel et al. with a recurrence of 50% in treatment of chronic pseudo-obstruction.³⁰ The use of epidural anesthesia as a block of excess sympathetic tone demonstrated a moderate response.

The best evidence of medical treatment is available for neostigmine. Based upon the presumed pathophysiology of ACPO, Huchingson and Griffith used neostigmine and guanethidine for ACPO.³¹ Neostigmine is an anticholinesterase that inhibits acetylcholinesterase to allow increase in synaptic levels of acetylcholine.

Multiple prospective studies have validated the use of neostigmine in ACPO.^{32–36} Patients had improvement in symptoms with only occasional mild side effects such as

sweating and transient bradycardia. Recurrence rate range from 0 to 33%.

The optimal dose of neostigmine and administration technique remains debatable. A dose of 2–2.5 mg bolus over 3–5 minutes intravenously was found to be successful in 80% of the patients after the first dose.²⁵ The onset of action of intravenous neostigmine is 20–30 minutes. It can be used 2–3 times in 24 hours, if satisfactory response is not seen after first dosing.³⁷ If the second or third dose of neostigmine fails to resolve the problem, the patient should proceed for more aggressive measures of decompression. White et al. described a protocol in a patient refractory to three doses of bolus neostigmine. They mixed 5 mg of neostigmine in 50 mL normal saline solution and infused at a rate of 0.4 mg/h.³⁸ An overall positive response was observed in 19 out of 24 patients at a continuous infusion rate of 0.4–0.8 mg/h of neostigmine in a randomized study performed by van Der Spoel et al.³⁹

Side effects with neostigmine were common in all the trials and is one of the reasons for exclusion of patients from those trials. Low heart rates, low systolic blood pressures, and signs of perforation including peritoneal signs of free air were among the commonest reasons for exclusion. All patients receiving neostigmine should be monitored and atropine should be available at the bedside to counter neostigmine induced bradycardia. Contraindications to neostigmine include known hypersensitivity and mechanical urinary or intestinal obstruction. Relative contraindications include β -blocker therapy, bradycardia, asthma, acidosis, myocardial infarction, or peptic ulcer disease.⁴⁰

Oral neostigmine is not recommended in ACPO because of its erratic absorption in the GI tract. Relapse after successful treatment with neostigmine has been observed in 17–38% in different studies.^{41–43}

Polyethylene glycol (PEG) has been shown to prevent recurrence. A randomized placebo control study conducted by Sgouros et al. suggested that there is no recurrence of distention versus 33% in placebo group when balance solution of PEG given orally after successful decompression with neostigmine or colonoscopy.⁴⁴

A prospective randomized study conducted by O'Dea et al. observed a positive response with 10–30 mg of pyridostigmine two times daily orally in patients who failed previous treatment with neostigmine and endoscopic decompression and also less severe side effects compared with neostigmine.⁴⁵

Methylnaltrexone, a new opioid receptor antagonist, has been found to have a potential role in narcotic induced ACPO.⁴⁶ It was tried after a failed treatment with neostigmine. Another new receptor antagonist, alvimopan, has been found to have a potential role in postgastrointestinal surgery induced ACPO.⁴⁷ Further studies are needed to establish the efficacy and safety of new receptor antagonist mentioned above as they may prove beneficial in treatment and prophylaxis of opioid induced ACPO.

Diatrizoate meglumine enema in relieving colonic distention was assessed in 18 patients in whom 78% of patients were found to be successfully decompressed.²⁰ The mechanism is thought to be due to hyperosmolality of the enema increasing intracolonic fluid.

In patients not responding to maximal supportive and pharmacological therapy and without signs of ischemia and perforation, endoscopic decompression should be considered (Fig. 1).

Endoscopic Decompression

In the year 1997, Kukora and Dent first time described the colonic decompression of ACPO. Out of 6 patients, 5 were successfully treated with this method without any recurrence.⁴⁸ Colonoscopy was the second line treatment in patients not responding to conservative measures prior to introduction of neostigmine. Colonoscopy for ACPO is performed without oral laxatives or bowel preparation. Sedation in the form of benzodiazepines is recommended. Narcotics are avoided in view of their property to inhibit colonic activity. Recurrences after colonoscopic decompression remain problematic, it has been reported in up to 40% of patients.⁴⁹ In patients with recurrence, a repeated colonic decompression was achieved in 56–87% but with higher rates of subsequent cecal distention. Use of tube decompression improves the overall success of decompression if placed in an area affected by ACPO.^{50,51} The tube is placed over a guide wire advanced through a colonoscope. After loading the guide wire in appropriate place, the colonoscope is withdrawn with regular suction, following which a decompression tube is passed into the colon over the guide wire under fluoroscopy guidance. The decompression tube should be placed to gravity drainage and flushed every 4–6 hours to prevent clogging. In a series of 50 patients who underwent endoscopic decompression and tube placement, success rate was observed in 88% of patients. About 80% success rate was observed in patients receiving tube decompression after endoscopy as compared to 25% success in those where tube decompression was not used.¹⁸ In another study conducted by Harig et al., 4 out of 9 patients had recurrence in the only colonoscopic group, whereas none had recurrence out of 11 in colonoscopy plus tube decompression group.⁵²

Placement of a percutaneous endoscopic tube is another advanced endoscopy technique known as percutaneous endoscopy colostomy of the cecum. It can be performed either through a combined endoscopic and radiology approach or in a manner analogous to placement of percutaneous endoscopy gastrostomy tube.^{53,54} It is considered to be safe and effective procedure in the hands of an experienced endoscopist. Various techniques have been described for doing this procedure, but there are no studies to establish superiority of one method over another. The choice of technique depends on the preference of the

endoscopist. This approach may prove useful for patients who are not responding to maximal medical and endoscopic management and are poor surgical candidates.

Surgical Intervention

Surgical options include cecostomy or colostomy. Acute colonic pseudo-obstruction is one of the few indications for cecostomy. Cecostomy is performed by limited laparotomy with a small incision overlying the cecum. Laparoscopic cecostomy has the potential additional benefit of visualization of entire colon to diagnose unsuspected ischemia or infarction, but it is challenging in patients with massively dilated colon with huge abdominal distention.⁵⁵ Laparotomy is indicated for ischemia, perforation, or if the diagnosis is not clear. The diagnosis of colonic ischemia is clinical as suggested by changes in perceived pain, physical examination finding, and laboratory and imaging data. Lactic acidosis, fever, abdominal pain, and leukocytosis raise the suspicion of mucosal ischemia. The CT scan often shows nonspecific colonic wall thickening and pericolic fat stranding.⁵⁶ Pneumatosis and/or gas in the mesenteric veins are ominous signs associated with bowel wall thickening and are mainly due to bowel infarction.⁵⁷ Sometimes, right hemicolectomy, and at others, total abdominal colectomy is also required depending upon the area affected. Mortality rate ranges from 35 to 60% with operative interventions. The high mortality associated with laparotomy due to ischemia and perforation warns for the need of early diagnosis, initiation of conservative management, and early surgical consultation.

CONCLUSION

Acute colonic pseudo-obstruction or Ogilvie syndrome is a clinical syndrome characterized by marked colonic distention without evidence of mechanical obstruction; it complicates the hospital stay of acutely ill medical and surgical patients. It carries a poor prognosis if early identification and management is not instituted. Exact pathophysiology remains debatable. There is no effective prevention for this problem. High clinical suspicion and appropriate use of imaging techniques differentiates ACPO from other causes of mechanical obstruction of colon. Initial conservative therapy successfully resolves ACPO in majority of patients. Neostigmine remains the drug of choice in patients with failed response to conservative management. Advances in endoscopic management also reduce the need of surgical intervention. Newer therapies include oral pyridostigmine and new opioid receptor antagonist as a potential agent for nonresponders. Advanced colonoscopic technique with tube decompression provides alternative options for decompression. Percutaneous cecostomy may be a safe option in experienced hands. In the presence of peritoneal signs or perforation, surgery is the appropriate intervention.

REFERENCES

- Ogilvie H. Large-intestine colic due to sympathetic deprivation; a new clinical syndrome. *BMJ*. 1948;2(4579):671-3.
- Dudley HAF, Paterson-Brown S. Pseudo-obstruction. *Br Med J (Clin Res Ed)*. 1986;292(6529):1157-8.
- Dudley HAF, Sinclair IS, McLaren IF, et al. Intestinal pseudo-obstruction. *J R Coll Surg Edinb*. 1958;3(3):206-17.
- Nanni G, Garbini A, Luchetti P, et al. Ogilvie's syndrome (acute colonic pseudo-obstruction): review of the literature (October 1948 to March 1980) and report of four additional cases. *Dis Colon Rectum*. 1982;25(2):157-66.
- Rex DK. Colonoscopy and acute colonic pseudo-obstruction. *Gastrointest Endosc Clin N Am*. 1997;7(3):499-508.
- Jeffcoate WJ. Should eponyms be actively detached from diseases? *Lancet*. 2006;367(9519):1296-7.
- Saunders MD. Acute colonic pseudo-obstruction. *Best Pract Res Clin Gastroenterol*. 2007;21(4):671-8.
- Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome): an analysis of 400 cases. *Dis Colon Rectum*. 1986;29:203-10.
- Moons V, Coremans G, Tack J. An update on acute colonic pseudo-obstruction (Ogilvie's syndrome). *Acta Gastroenterol Belg*. 2003;66:150-3.
- Durai R. Colonic pseudo-obstruction. *Singapore Med J*. 2009;50(3):237-44.
- Vanderwinden JM. Role of interstitial cells of Cajal and their relationship with the enteric nervous system. *Eur J Morphol*. 1999;37(4-5):250-6.
- Jain D, Moussa K, Tandon M, et al. Role of interstitial cells of Cajal in motility disorders of the bowel. *Am J Gastroenterol*. 2003;98(3):618-24.
- Akiho H, Ihara E, Motomura Y, et al. Cytokine-induced alterations of gastrointestinal motility in gastrointestinal disorders. *World J Gastrointest Pathophysiol*. 2011;2(5):72-81.
- Davis L, Lowman RM. An evaluation of cecal size in impending perforation of the cecum. *Surg Gynecol Obstet*. 1956;103(6):711-8.
- Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med*. 1999;341:137-41.
- Geller A, Petersen BT, Gostout CJ. Endoscopic decompression for acute colonic pseudo-obstruction. *Gastrointest Endosc*. 1996;44:144-50.
- Kaiser AM. Ogilvie transition to colonic perforation. *Am J Surg*. 2010;200(1):e15-6.
- Saunders MD, Kimmey MB. Systematic review: acute colonic pseudo-obstruction. *Aliment Pharmacol Ther*. 2005;22(10):917-25.
- Godfrey EM, Addley HC, Shaw AS. The use of computed tomography in the detection and characterisation of large bowel obstruction. *N Z Med J*. 2009;122(1305):57-73.
- Schermer CR, Hanosh JJ, Davis M, et al. Ogilvie's syndrome in the surgical patient: a new therapeutic modality. *J Gastrointest Surg*. 1999;3(2):173-7.
- Beattie GC, Peters RT, Guy S, et al. Computed tomography in the assessment of suspected large bowel obstruction. *ANZ J Surg*. 2007;77(3):160-5.
- Jacob SE, Lee SH, Hill J. The demise of the instant/unprepared contrast enema in large bowel obstruction. *Colorectal Dis*. 2008;10(7):729-31.
- Jain A, Vargas HD. Advances and challenges in the management of acute colonic pseudo-obstruction (Ogilvie syndrome). *Clin Colon Rectal surg*. 2012;25(1):37-45.
- De Giorgio R, Knowles CH. Acute colonic pseudo-obstruction. *Br J Surg*. 2009;96(3):229-39.
- Harrison ME, Anderson MA, Appalaneni V, et al; ASGE Standards of Practice Committee. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. *Gastrointest Endosc*. 2010;71(4):669-79.
- Wegener M, Börsch G. Acute colonic pseudo-obstruction (Ogilvie's syndrome). Presentation of 14 of our own cases and analysis of 1027 cases reported in the literature. *Surg Endosc*. 1987;1(3):169-74.
- Delgado-Aros S, Camilleri M. Pseudo-obstruction in the critically ill. *Best Pract Res Clin Gastroenterol*. 2003;17:427-44.
- Bonacini M, Smith OJ, Pritchard T. Erythromycin as therapy for acute colonic pseudo-obstruction (Ogilvie's syndrome). *J Clin Gastroenterol*. 1991;13(4):475-6.

29. Lipton AB, Knauer CM. Pseudo-obstruction of the bowel. Therapeutic trial of metoclopramide. *Am J Dig Dis.* 1977;22(3):263-5.
30. Emmanuel AV, Shand AG, Kamm MA. Erythromycin for the treatment of chronic intestinal pseudo-obstruction: description of six cases with a positive response. *Aliment Pharmacol Ther.* 2004;19(6):687-94.
31. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl.* 1992;74(5):364-7.
32. Amaro R, Rogers AL. Neostigmine infusion: new standard of care for acute colonic pseudo-obstruction? *Am J Gastroenterol.* 2000;95:304-5.
33. Trevisani GT, Hyman NH, Church JM. Neostigmine: safe and effective treatment for acute colonic pseudo-obstruction. *Dis Colon Rectum.* 2000;43:599-603.
34. Loftus CG, Harewood GC, Baron TH. Assessment of predictors of response to neostigmine for acute colonic pseudo-obstruction. *Am J Gastroenterol.* 2002;97:3118-22.
35. Stephenson BM, Morgan AR, Salaman JR, et al. Ogilvie's syndrome: a new approach to an old problem. *Dis Colon Rectum.* 1995;38:424-7.
36. Turego-Fuentes F, Munoz-Jimenez F, Del Valle-Hernandez E, et al. Early resolution of Ogilvie's syndrome with intravenous neostigmine. *Dis Colon Rectum.* 1997;40:1353-7.
37. Paran H, Silverberg D, Mayo A, et al. Treatment of acute colonic pseudo-obstruction with neostigmine. *J Am Coll Surg.* 2000;190(3):315-8.
38. White L, Sandhu G. Continuous neostigmine infusion versus bolus neostigmine in refractory Ogilvie syndrome. *Am J Emerg Med.* 2011;29(5):576.e1-3.
39. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, et al. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure—a prospective, double-blind, placebo-controlled trial. *Intensive Care Med.* 2001;27(5):822-7.
40. Eisen GM, Baron TH, Dominitz JA, et al. Acute colonic pseudo-obstruction. *Gastrointest Endosc.* 2002;56:789-92.
41. Ponc R, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med.* 1999;341(3):137-41.
42. Stephenson BM, Morgan AR, Salaman JR, et al. Ogilvie's syndrome: a new approach to an old problem. *Dis Colon Rectum.* 1995;38(4):424-7.
43. Mehta R, John A, Nair P, et al. Factors predicting successful outcome following neostigmine therapy in acute colonic pseudo-obstruction: a prospective study. *J Gastroenterol Hepatol.* 2006;21(2):459-61.
44. Sgouros SN, Vlachogiannakos J, Vassiliadis K, et al. Effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudo obstruction after resolution of colonic dilation: a prospective, randomised, placebo controlled trial. *Gut.* 2006;55(5):638-42.
45. O'Dea CJ, Brookes JH, Wattchow DA. The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine. *Colorectal Dis.* 2010;12(6):540-8.
46. Thomas J, Karver S, Cooney GA, et al. Methylxanthone for opioid-induced constipation in advanced illness. *N Engl J Med.* 2008;358(22):2332-43.
47. Holzer P. Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects. *Curr Opin Anaesthesiol.* 2010;23(5):616-22.
48. Kukora JS, Dent TL. Colonic decompression of massive nonobstructive cecal dilation. *Arch Surg.* 1977;112:512-7.
49. Gosche JR, Sharpe JN, Larson GM. Colonoscopic decompression for pseudo-obstruction of the colon. *Am Surg.* 1989;55:111-5.
50. Sarioglu J, Matsumoto T, Kerstein MD. Colonoscopically guided tube decompression in Ogilvie's syndrome. *Dis Colon Rectum.* 1991;34:720-2.
51. Fausel CS, Goff JS. Nonoperative management of acute idiopathic colonic pseudo-obstruction (Ogilvie's syndrome). *West J Med.* 1985;143:50-4.
52. Harig JM, Fumo DE, Loo FD, et al. Treatment of acute nontoxic megacolon during colonoscopy: tube placement versus simple decompression. *Gastrointest Endosc.* 1988;34(1):23-7.
53. Baraza W, Brown S, McAlindon M, et al. Prospective analysis of percutaneous endoscopic colostomy at a tertiary referral centre. *Br J Surg.* 2007;94(11):1415-20.
54. Lynch CR, Jones RG, Hilden K, et al. Percutaneous endoscopic cecostomy in adults: a case series. *Gastrointest Endosc.* 2006;64(2):279-82.
55. Duh QY, Way LW. Diagnostic laparoscopy and laparoscopic cecostomy for colonic pseudo-obstruction. *Dis Colon Rectum.* 1993;36(1):65-70.
56. Bullard KM, Dunn RD. Colon, rectum, and anus. In: Brunicki FCAD, Billiar TR, Dunn DL, et al. (Eds). *Schwartz's Principles of Surgery.* 9th edition. New York: McGraw-Hill; 2010. pp. 1058.
57. Theodoropoulou A, Koutroubaki IE. Ischemic colitis: clinical practice in diagnosis and treatment. *World J Gastroenterol.* 2008;14(48):7302-8.

Acid Suppression in Critically Ill: Is It Really Necessary?

Samir Sahu

INTRODUCTION

Gastric mucosa is sensitive to changes in hemodynamics such as hypotension resulting in reduced perfusion and cytokine-mediated inflammation. This results in stress-related mucosal disease (SRMD), which endoscopically may range from superficial erosions to multiple ulcers and can lead to clinically important bleeding episodes requiring blood transfusion.¹ Prophylaxis of such lesions is nowadays available both as proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA). Both of these agents are well tolerated and are able to decrease incidence of bleeding episode.² In spite of these pharmacological agents, stress ulcer prophylaxis (SUP) measures and decrease in bleeding episode has not been translated into mortality benefit in prospective studies. Thus, recently, some intensivists have expressed concerns about the safety of SUP, especially with respect to infectious complications.

EPIDEMIOLOGY

Stress-related mucosal disease is present in most critically ill patients, but only a few patients experience overt bleeding complications. Only around 1% of them develop SMRD-related gastrointestinal (GI) bleeding.^{2,3}

PATHOPHYSIOLOGY

Both systemic hypotension due to absolute or relative hypovolemia, cardiogenic or obstructive shock, use of vasopressors and local splanchnic hypoperfusion due to positive end expiratory pressure in patients on mechanical ventilation, may lead to decrease in gastric mucosal blood flow. Hypoperfusion leads to a reduced production of several protective mechanisms that exist in a healthy stomach. These mechanisms can cause mucosal damage, but need the presence of gastric acid to cause major ulcerations and gastric bleeding. Without acid, mucosal damage is only

minimal. This is the rationale for the use of acid-suppressive drugs such as PPI or H2RA for pharmacological prophylaxis.⁴

Recent studies report a very low incidence of stress ulcer-related bleeding due to effective pharmacological and nonpharmacological prophylactic measures, therefore risk of mortality appears to be low.²

Main risk factors for bleeding are mechanical ventilation for more than 48 hours, coagulopathy [international normalized ratio (INR) > 1.5 or platelet count (PLT) < 50/ μ L or prothrombin time (PTT) > 2 \times Upper Limit of Normal (ULN)] (Gr A evidence), cardiogenic shock, burn patients, those with craniocerebral injury, acute renal failure (Gr B evidence) and history of an upper gastrointestinal bleeding within the past 12 months, severe sepsis or septic shock, known peptic ulcer disease, post-kidney or liver transplantation and those patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) or high-dose glucocorticoids (Gr C evidence). Based upon current evidence, these patients should receive pharmacological ulcer prophylaxis.⁴

Almost universal use of stress ulcer prophylaxis in intensive care unit (ICU) is due to the above mentioned risk factors, which are present in many of the critically ill patients. Many observational studies have reported use of SUP in more than 80% of critically ill patients.³

Due to the fact that acid-suppressive medications can effectively lower the SRMD-related bleeding, which are clinically important as shown in many meta-analyses, though based on low-quality studies, national and international guidelines have endorsed this practice in patients with risk factors for bleeding.⁵ There are several trials and meta-analyses comparing PPI to H2RA. Most of them favor PPI with respect to reduction of bleeding rates. PPI are the agents of choice in SUP.²

ADVERSE EFFECTS

We ingest pathogens during routine feed and gastric acid acts as a natural barrier against these pathogens. Suppression of

this acid barrier by pharmacological means takes away this defense mechanism. This leads to overgrowth of bacteria in upper GI tract. This phenomenon is more evident with agents with stronger and longer acid-suppressing effect like PPI. Moreover, acid-suppressing agents can also alter leukocyte function. This results in both intestinal infections such as *Clostridium difficile*-associated diarrhea (CDAD) and also to extraintestinal infections like pneumonia (via retrograde microaspiration).⁴ Of these infections, *C. difficile* is the most problematic one. *C. difficile* spores or vegetative form are transferred through lack of contact precautions and fecal oral route. The vegetative form is normally inhibited by gastric acid and spores are resistant to it. Suppression of this acid milieu (gastric pH >5) leads to increased survival of the vegetative forms, which are the main culprit in CDAD as the stool of infected individuals contains tenfold more vegetative forms than spores. Due to the same reason, frequent CDAD relapses and recurrent diseases are more common in patients on PPI therapy.^{3,4}

The role of acid suppression as a risk factor for pneumonia is unclear but remains likely. Larger randomized prospective trials are warranted to resolve this issue.³

Patients with liver cirrhosis are prone to adverse effects of SUP. Use of PPI was an independent risk factor for overall mortality. This might be due to an increased risk of spontaneous bacterial peritonitis and higher rates of pneumonia and CDAD.⁶

Due to polypharmacy, there are important drug-drug interactions with PPI, one of the most important clinically, is between the antiplatelet agent clopidogrel and various PPI. A study reported increased cardiovascular events in patients taking both clopidogrel and PPI.⁷ Moreover, use of PPI has been associated with liver toxicity manifesting as transaminitis, bone marrow suppression manifesting as thrombocytopenia and hypomagnesemia.⁴

Enteral nutrition seems to be protective against stress ulcer-related bleeding and addition of a pharmacological SUP may not result in additional substantial benefit. This needs to be further explored in randomized prospective trials as enteral nutrition could be a viable alternative to pharmacological SUP.^{8,9} It was observed that in enterally fed patients, who have additional SUP therapy, the incidence of pneumonia was increased compared to patients on parenteral nutrition. In this subgroup, an increase in mortality was also observed.¹⁰

CONCLUSION

The triad of stress-related increased gastric acid formation, reduced perfusion of GI mucosa due to sepsis or shock and reduction of protective mucosal barrier make the critically ill patients more vulnerable to GI bleed due to SRMD or ulcer. This leads to almost universal application of pharmacological prophylaxis in the majority of ICU patients at present, with PPI or H2RA effectively preventing GI bleeding. Though this common practice has not resulted in decreases mortality and its universal use is questioned as this practice may be associated with some risk. Nosocomial pneumonia and *C. difficile* are among the two most serious association of this practice. Thus risk benefit needs to be balanced carefully before selecting SUP. Other less risky strategies like early enteral feeding or restricting SUP to very high-risk patients during early ICU stay, needs to be evaluated in prospective randomized trials.

REFERENCES

1. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care*. 2005;20:35-45.
2. Alhazzani W, Alenezi F, Jaeschke RZ, et al. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med*. 2013;41:693-705.
3. Buendgens L, Koch A, Tacke F. Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis. *World J Crit Care Med*. 2016;5:57-64.
4. MacLaren R, Jarvis CL, Fish DN. Use of enteral nutrition for stress ulcer prophylaxis. *Ann Pharmacother*. 2001;35:1614-23.
5. Lin PC, Chang CH, Hsu PI, et al. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med*. 2010;38:1197-205.
6. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2014;40:11-22.
7. Buendgens L, Bruensing J, Matthes M, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. *J Crit Care*. 2014;29:696.e11-696.e15.
8. Deshpande A, Pasupuleti V, Thota P, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol*. 2013;28:235-42.
9. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301:937-44.
10. Marik PE, Vasu T, Hirani A, et al. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med*. 2010;38:2222-8.

Section 4

Infectious Diseases

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Sepsis 3: What's New?

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INTRODUCTION^{1,2}

The Greeks first described sepsis in 700 BC as an infection leading to organ decomposition and death. Sepsis, an inflammatory response to infection, is a leading cause of admission to hospital. Worldwide, every minute a patient presents to an emergency department with severe sepsis or septic shock; the mortality for this condition ranges from 25 to 50%. While mortality in hospital is probably decreasing in the developed countries, long-term mortality after sepsis has remained high as many patients die in the subsequent months. Sepsis and septic shock kill one in four (and often more) and is increasing in incidence. Similar to other acute events like polytrauma, acute myocardial infarction, or stroke, the rapidity with which the therapy is administered in the initial hours of sepsis is likely to influence outcome.

DEFINITION³⁻¹⁴

In a 1992 consensus conference, the American College of Chest Physicians and the Society of Critical Care Medicine in a joint statement defined sepsis as a continuum syndrome and introduced the term systemic inflammatory response syndrome (SIRS), which does not require the presence of infection. Sepsis was defined as suspected or proven infection plus a SIRS (e.g., fever, tachycardia, tachypnea, and leukocytosis). Severe sepsis was defined as sepsis with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia, or obtundation). Septic shock was defined as severe sepsis with hypotension, despite adequate fluid resuscitation. Septic shock and multiorgan dysfunction are the most common causes of death in patients with sepsis.

The 2001 International Sepsis Definition Conference attempted to improve on the specificity of these definitions by elaborating common clinical and laboratory manifestations of the disorder. One of the goals of creating these definitions

was to help physicians recognize patients at risk for severe sepsis and initiate therapy promptly. In order to reflect the many prognostic factors in sepsis and provide a hypothesis-generating model for future research, the PIRO (Predisposing factors, nature of Insult, intensity of Response, number of Organ dysfunction) grading system was also proposed.

The septic response is an extremely complex cascade of events, including proinflammatory, anti-inflammatory, humoral, cellular, and circulatory involvement. There are inherent challenges in defining sepsis and septic shock. First and foremost, sepsis is a broad term applied to an incompletely understood process. There are, as yet, no simple and unambiguous clinical criteria or biological, imaging or laboratory features that uniquely identify a septic patient. As such the definitions of sepsis have been largely unchanged for more than two decades.

There was an urgent need of revised definition of sepsis due to the following reasons:

- Emphasizing in the definition that sepsis is a severe entity with a much poor prognosis than uncomplicated infection, that is to say the term sepsis itself should denote severity
- Recognizing that at present there is not a validated standard diagnostic test, leading to major variations in reported incidence and mortality rates of sepsis
- Identify simple, inexpensive, bedside criteria for identifying all elements of sepsis like presence of an infection, type of host response, and organ dysfunction
- Provide a more consistent epidemiological definition of sepsis.

The European Society of Intensive Care Medicine and The Society of Critical Care Medicine convened a task force of 19 critical care, infectious disease, and surgical and pulmonary specialists in January 2014 and published the "Third International Consensus Definitions for Sepsis and Septic Shock" (Sepsis-3). The recommendation of the task force was circulated to the major international societies for

endorsement. The task force recommended that the new definition be designated as Sepsis-3. Sepsis-1 and Sepsis-2 were the terminology given to 1991 and 2001 statements, respectively, to emphasize the need for future iterations.

CHALLENGES

The absence of a gold standard diagnostic test for sepsis resulting in a limited definition of constellation of clinical signs and symptoms in a patient with suspected infection is one of the biggest challenge in sepsis research. The concept of SIRS may be present in the absence of infection in many critically ill patient. The use of two or more SIRS criteria to identify sepsis has been decided arbitrarily in the previous definition and was found to be unhelpful. One in eight critically ill patients with infection will not have a minimum of two SIRS criteria. Sequential Organ Failure Assessment (SOFA) score¹⁵ (Table 1) is the current standard to assess severity of organ dysfunction and indicates poor prognosis with increasing score. Simply put, the higher the SOFA score, the increased probability of mortality. One of the limitations of this test is requirement of multiple laboratory test thus routine application may be difficult universally.

RECOMMENDATIONS

The present task force recommends sepsis to be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. An increase in SOFA score by two points from baseline (or zero, if baseline not known) is identified as new organ dysfunction as this reflects a chord with poor prognosis and an overall mortality of >10% in this population.

SCREENING PATIENTS LIKELY TO HAVE SEPSIS

Three simple bedside criteria were validated to identify patients with suspected infection who are at increased risk of deterioration. These are altered mental status, systolic blood pressure ≤ 100 mmHg and/or respiratory rate ≥ 22 /min (presence of any two) this is called quick SOFA or qSOFA. Though this is less robust in identifying this patient population in ICU than SOFA, but can be used in the emergency department and wards repeatedly.

The term septic shock refers to patient with sepsis and persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mmHg and having a serum lactate level more than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. In this cohort, the hospital mortality is more than 40%.

CONTROVERSIES/LIMITATIONS

The current recommendations of the task force can be seen as pragmatic compromises and general abilities of this poorly understood complex process. In all sepsis definitions, the diagnosis of sepsis depends on whether the patient has "suspected infection". Unfortunately, there is little discussion about exactly how to determine whether infection is "suspected". Indeed, for most patients presenting with an unclear problem, infection is the differential diagnosis. Quick SOFA and SOFA are mortality predictors and not tests for identifying infection or sepsis. Although qSOFA is validated in retrospective studies to identify early sepsis it still needs to be validated prospectively and in various clinical setting with variable infrastructure. Absence

TABLE 1 Sequential Organ Failure Assessment score*

SOFA Score	0	1	2	3	4
Respiratory (PaO ₂ /FiO ₂ mmHg)	>400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation (platelets $\times 10^9$ /L)	>150	<150	<100	<50	<20
Liver (bilirubin μ mol/L)	<20	20–32	33–101	102–204	>204
CVS (hypotension)	MAP >70 mmHg without vasopressor or inotrope	MAP <70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine >5 or nor/adrenaline ≤ 0.1	Dopamine >15 or nor/adrenaline >0.1
CNS (Glasgow Coma Score)	15	13–14	10–12	6–9	<6
Renal (creatinine mmol/L or UOP)	<0.11	0.11–0.17	0.171–0.299	0.30–0.44 or UOP <500 mL/day	>0.44 or UOP <200 mL/day

SOFA, sequential organ failure assessment; CVS, cardiovascular system; MAP, mean arterial pressure; CNS, central nervous system; UOP, urinary output.

*Based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

of two or more SOFA or qSOFA criteria should not deter investigation for identifying underlying sepsis, if clinically indicated. Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new onset organ dysfunction, any unexplained organ dysfunction should thus raise the possibility of underlying infection. Sepsis-3 recognizes the universal possibility of infection in undifferentiated patients. Defining "suspected infection" so broadly renders this criterion nearly meaningless. Quick SOFA has similar performance compared to SIRS for mortality prediction. In order to simplify, lactate measurement was not incorporated in the definition, but it should be utilized as a guide to monitor therapeutic response. Further work need to be done to develop similar definitions for pediatric populations. Validation of these recommendations should be carried out in low- and middle-income countries for justifying its universal application.

Recently, a trio of trials ProCESS (Protocol-based Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis Evaluation) and ProMISe (Protocolized Management in Sepsis), while reporting an all-time low-sepsis mortality, question the continued need for all of the elements of early goal-directed therapy or the need for protocolized care for patients with severe and septic shock.¹⁶⁻²⁰ An in-depth analysis of these trials taking into consideration the current definition need to be implemented.

CONCLUSION

The current recommendation emphasizes new concept of the nonhomeostatic host response to infection as the basic pathophysiology of sepsis. The SIRS criteria were recognized to be nonspecific and overtly sensitive are considered overly nonspecific and of poor clinical utility. While recognition and treatment of the infectious trigger remain important, managing associated organ dysfunction should be paid due attention.

Clinical utility of sepsis-3 definition remains largely unknown at present and SIRS criteria may still guide clinicians toward identifying an ongoing infectious process, but "severe sepsis" is no longer a part of the new classification. Hypotension and increased lactate level are the cornerstone for identifying patients with septic shock. This definition is regarded as a transitional statement by the task force with future iteration as the evidence evolves. The current recommendation of qSOFA is aimed at aiding practitioners in prehospital, emergency departments, and hospital wards to promptly recognize and treat septic patients, i.e., those infected patients with poor prognosis. This will encourage

practitioners to investigate for further organ dysfunction and triaging to proper facility to prevent further organ dysfunction.

REFERENCES

1. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *BMJ*. 2007;335(7625):879-83.
2. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-54.
3. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-55.
4. Levy MM, Fink MP, Marshall JC, et al. International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003;29(4):530-8.
5. Shankar-Hari M, Deutschman CS, Singer M. Do we need a new definition of sepsis? *Intensive Care Med*. 2015;41(5):909-11.
6. Shankar-Hari M, Bertolini G, Brunkhorst FM, et al. Judging quality of current septic shock definitions and criteria. *Critical care*. 2015;19(1):445.
7. Singer M, Deutschman CS, Seymour CW, et al. The Sepsis Definitions Task Force The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-10.
8. Seymour CW, Liu V, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-74.
9. Shankar-Hari M, Phillips G, Levy ML, et al. Assessment of definition and clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):775-87.
10. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med*. 2015;372(17):1629-38.
11. Zamboni M, Ceola M, Almeida-de-Castro R, et al. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster. *J Crit Care*. 2008;23(4):455-60.
12. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med*. 2010;38(2):367-74.
13. Beesley S, Lanspa M. Why we need a new definition of sepsis. *Ann Transl Med*. 2015;3(19):296.
14. Klein Klouwenberg PM, Ong DS, et al. Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. *Intensive Care Med*. 2012;38(5):811-9.
15. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-10.
16. Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Curr Opin Anaesthesiol*. 2008;21(2):128-40.
17. Lilly CM. The ProCESS Trial—a new era of sepsis management. *N Engl J Med*. 2014;370(8):1750-1.
18. Nguyen HB, Jaehne AK, Jayaprakash N, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Crit Care*. 2016;20(1):160.
19. ARISE Investigators, Anzics Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-506.
20. Mouncey PR, Osborn TM, Power GS, et al. (ProMISe) Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301-5.

Neurological Manifestations of Scrub Typhus: A Great Mimic

Rahul A Pandit

INTRODUCTION

The scrub typhus or tsutsugamushi disease is a life-threatening zoonotic disease. It is a mite-borne infectious disease caused by *Orientia tsutsugamushi* (previously called *Rickettsia tsutsugamushi*). The name derives from the type of vegetation (i.e., terrain between woods and clearings) that harbors the vector. The organism is an obligate intracellular gram-negative organism with five major serotypes. This disease was first described in Japan in 1899, and the term "tsutsugamushi" is derived from two Japanese words, *tsutsuga* meaning something small and dangerous and *mushi* meaning creature. The disease is transmitted by the bite of larval chiggers of the trombiculid mite, which is both a reservoir and vector for the disease. The larvae usually feed on rats and humans are infected accidentally. In India, many states are endemic to scrub typhus; namely, Tamil Nadu, Himachal Pradesh, Jammu, Puducherry, Andhra Pradesh, Kerala, Meghalaya, and others.^{1,2} Farmers accounted for approximately two-thirds of all reported cases. Incidence rates are highest in people aged 40–60 years of age, but young children had higher rates of infection than young adults. Approximately, 80% of cases occurred during summer and monsoon.

CLINICAL MANIFESTATIONS

Scrub typhus can present with diverse clinical presentations. Usually, the incubation period is around 6–20 days. In the first few days after the bite, fever and chills could be the first presenting symptom. Usually, by the first week patients develop two characteristic symptoms rash and eschar.

1. **Rash:** Approximately, one-half of all patients develop a characteristically nonpruritic, macular, or maculopapular rash. The rash typically begins on the abdomen and spreads to extremities. Face could be involved and petechiae may develop
2. **Eschar:** A painless papule often appears at the site of the infecting bite. Subsequently, central necrosis occurs

which leads to the formation of characteristic eschar with black crust.

Serious complications usually are seen in the second week of illness. Pneumonitis, shock, thrombocytopenia, hepatomegaly, pleural effusion, ascites, acute kidney injury (AKI), and acute respiratory distress syndrome^{3,4} are reported. However, it is the neurological complications, which mimic other diseases and affect the neurological system predominantly, is difficult to differentiate and often diagnosis of scrub typhus may be missed in these patients.

Neurological Manifestation

Scrub typhus invades and multiplies in the vascular endothelium and results in widespread vasculitis involving capillaries, arterioles, and small arteries. Autopsy findings in patients with scrub typhus have revealed focal hemorrhages, coagulative necrosis, and granulomatous inflammation in the brain parenchyma.⁵ More than 45 case studies and reports in the last 30 years have reported various neurological manifestations of scrub typhus across Asia and South East Asian peninsula. A variety of symptoms and signs have been reported in the studies (Box 1).

Box 1: Neurological manifestations of scrub typhus

Symptoms

- Direct central nervous system involvement
 - Altered sensorium
 - Meningitis
 - Meningoencephalitis
 - Encephalitis
 - Encephalopathy
 - Seizures
 - Rarely stroke
 - Intracranial hemorrhage
 - Quadriplegia
 - Coma
- Immune-mediated
 - Optic neuritis
 - Acute disseminated encephalomyelitis
 - Guillain-Barre syndrome
 - Mononeuritis multiplex
 - Brachial plexopathy
 - Isolated cranial nerve palsy

Scrub typhus involves both the central and peripheral nervous system. Hence, diagnosis is often a challenge. The central nervous system (CNS) involvement is seen more with epidemic typhus than with scrub typhus. The incidence of neurological manifestation is reported up to 83% of diagnosed cases of scrub typhus. The common complications include altered sensorium, agitation, motor weakness, encephalitis, meningoencephalitis, and seizures.⁶⁻⁸ Some case reports have reported intracerebral hemorrhage and infarction.⁹ Cranial nerve deficits are seen in up to 25% of patients who demonstrate neurological involvement. The common cranial nerve involved is optic, abducens, facial, and cochlear. Kang et al.¹⁰ reported up to 19% ear symptoms, with sensory neural hearing loss, otalgia, and tinnitus had been the predominant symptoms. The peripheral nervous system involvement was seen in the form of mononeuritis multiplex, brachial plexopathy, polyneuropathy, and myelitis.

Systemic Manifestations

Often the presenting symptoms may not be neurological. This may lead to the disease mimicking many other common tropical diseases. The common systemic manifestations are listed in box 2.

The systemic manifestations are seen in varied proportions. Fever has been invariably reported in almost all the patients. Almost one-third patients present with shock, hepatomegaly.¹¹ Thrombocytopenia is reported again in most of the patients, however, severe thrombocytopenia was seen only in 30% patients. Incidence of AKI and lymphadenopathy is been reported ranging from 30 to 65%. Eschar is not present in all the patients. Absence of eschar may be associated with increased mortality. Misra et al. found an association with severe hypoalbuminemia (<3 g/dL) and increased mortality in his group of patients.

Differential Diagnosis

In India, scrub typhus often presents similar to malaria, leptospirosis, dengue, and enteric fever. Many of this tropical illness have similar signs and symptoms. All of them are known to have neurological manifestations as well. In addition to these if a patient presents with predominant neurological involvement then it could be often confused

with viral or bacterial meningitis. Particularly in Indian subcontinent, tuberculous meningitis could present with CNS vasculitis picture and it is often important to think scrub typhus as a differential diagnosis.

Often an acute high-grade fever presentation is seen in patients with scrub typhus. As with most rickettsial infections rash is present. However, fever and rash is also seen in dengue, as well as leptospirosis patients. Most viral encephalitis would present with high-grade fever, altered level of consciousness and possible rash. Though, it may be difficult to clinically differentiate between dengue and leptospirosis, both have a high specificity and sensitivity antibody test, which is easily available and gives a rapid result. To differentiate from meningoencephalitis is a clinical dilemma. Presence of thrombocytopenia (<100,000/mm³), multisystem involvement especially acute lung injury and AKI are usually pointers towards scrub typhus.¹² Relative bradycardia is often seen in patients with *Orientia tsutsugamushi* infection. It is defined as an increase of <10 beats/min/increase in temperature by 1°C. Relative bradycardia is also seen up to 73% of enteric fever cases and also reported in Legionnaires disease and infections caused by Chlamydia.¹³

INVESTIGATIONS

Blood Test

All patients who present with a suspicion of scrub typhus in endemic areas should have a complete blood count, renal function test, and liver function test done. In addition, malaria, dengue, and leptospirosis should be ruled out as well. A rapid antigen test for dengue along with an antibody testing is readily available. Similarly, for leptospirosis, antibody testing is sensitive. For malaria, thin and thick smear examination of blood along with a rapid antigen test gives a good sensitivity and specificity.

Traditionally, Weil-Felix test has been widely used to diagnose scrub typhus, however, the Weil-Felix test suffers from poor sensitivity and specificity with studies showing an overall sensitivity as low as 33% and specificity of 46%. It has been now widely replaced by indirect fluorescent antibody test. A single measurement may be used if the titers are greater than 1:50. However, a conclusive diagnosis is made if there is a fourfold increase in titer in paired samples collected at least 14 days apart.¹⁴

Imaging

Magnetic resonance imaging (MRI) has widely replaced computerized tomography (CT) as an investigation of choice in patients presenting with neurological involvement. Unfortunately, the MRI findings in scrub typhus are not specific and often MRI may be normal. There are reports of meningeal enhancement seen on MRI and some cases have also shown white matter lesions with diffusion restriction

Box 2: Systemic manifestation of scrub typhus

Signs and symptoms of systemic manifestations

- | | |
|----------------------|---------------------|
| • Fever | • Myalgia |
| • Rash | • Thrombocytopenia |
| • Eschar | • Hypoalbuminemia |
| • Vomiting | • Renal dysfunction |
| • Lymphadenopathy | • Liver dysfunction |
| • Hepatosplenomegaly | • Leucocytosis |

pattern.¹¹ Misra et al. in a large study demonstrated that only one patient had an abnormal MRI. Other complications like hemorrhage, infarction or acute disseminated encephalomyelitis could be picked up on MRI but are not pathognomic of scrub typhus.

Apart from MRI, an X-ray of chest is often requested to assess the lung status and depending on the systemic involvement CT scan of chest or abdomen could be done. myocarditis and shock are often seen in these patients. A transthoracic two-dimensional echocardiogram is often informative in diagnosing the problem and also helps in guiding therapy, fluids, and vasoactive medications.

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) has been extensively studied in patients with scrub typhus. The limitation to CSF examination could be severe thrombocytopenia and coagulopathy due to disease. Cerebrospinal fluid is examined for cell count, proteins, glucose, adenosine deaminase (ADA) level, and nested polymerase chain reaction (PCR) study for herpes simplex, Japanese encephalitis and for *Rickettesia* PCR (if available).

The CSF often demonstrates lymphocytic pleocytosis (40–120/mm³) along with high-proteins (>60 mg/dL) and moderately reduced glucose. The findings are often confused with tuberculosis meningitis (TBM); CSF ADA has shown to have a good specificity and sensitivity to diagnose TBM from other diseases. An absolute CSF ADA level >10 would be indicative of TBM rather than scrub typhus.¹⁵

Electroencephalogram

Electroencephalogram (EEG) is often used to rule out seizure activity and nonconvulsive states, EEG helps in establishing a diagnosis of convulsions and early treatment. Misra et al.¹¹ demonstrated a generalized slowing in theta to delta range, but no focal slowing, asymmetry, or epileptiform activity in his group of patients. Status epileptus has also been reported in a small subset of scrub typhus patients but it has been shown to have a good outcome with treatment.

COURSE

Scrub typhus lasts for 14–21 days without treatment. Interstitial pneumonia, pulmonary edema, congestive heart failure, circulatory collapse, and a wide array of signs and symptoms of CNS dysfunction may complicate severe infections. Death may occur as a result of these complications, usually late in the second week of the illness.

TREATMENT

Doxycycline remains the main drug for treatment of scrub typhus. Administered in a dose of 100 mg twice daily for

7 days has shown to be effective in treating most of the patients. In patients who have a severe form of disease (multiorgan involvement), addition of azithromycin in dose of 500 mg once daily for 3–7 days had been advocated. In some patients with neurological involvement, doxycycline may not be sufficient as it is a bacteriostatic drug and does not cross blood-brain barrier. In such patients, addition of rifampicin may be beneficial. In pregnancy, azithromycin is preferred to avoid the tetracycline group. Chemoprophylaxis can be taken if visiting endemic areas with doxycycline 200 mg once a week until staying in endemic area.

CONCLUSION

Scrub typhus neurological involvement is a less of complication compared to respiratory or gastrointestinal problems. It is associated with altered sensorium or cranial nerve deficits and generally resolves completely with doxycycline therapy. Due to the presence of lymphocytic pleocytosis with increased CSF protein, TBM is a close differential diagnosis. This may result in rifampicin based anti-TB therapy, masking the diagnosis of scrub typhus and sometimes results in patients continuing long-term therapy for TBM.

REFERENCES

1. Mathai E, Rolain JM, Verghese GM, et al. Outbreak of scrub typhus in southern India during the cooler months: Ann N.Y. Acad. Sci. 2003;990:359–64.
2. Sharma A, Mahajan S, Gupta ML, et al. Investigation of an outbreak of scrub typhus in the himalayan region of India. Jpn J Infect Dis. 2005;58(4):208–10.
3. Sittiwangkul R, Pongprot Y, Silvilarat S, et al. Acute fulminant myocarditis in scrub typhus. Ann Trop Paediatr. 2008;28(2):149–54.
4. Tsay RW, Chang FY. Acute respiratory distress syndrome in scrub typhus. QJM. 2002;95(2):126–8.
5. Settle EB, Pinkerton H, Corbett AJ. A pathologic study of tsutsugamushi disease (scrub typhus) with notes on clinicopathologic correlation. J Lab Clin Med. 1945;30:639–61.
6. Mahajan SK, Rolain JM, Kanga A, et al. Scrub typhus involving central nervous system, India, 2004–2006. Emerg Infect Dis. 2010;16(10):1641–3.
7. Kim JH, Lee SA, Ahn TB, et al. Polyneuropathy and cerebral infarction complicating scrub typhus. J Clin Neurol. 2008;4(1):36–9.
8. Yang SH, Wang LS, Liang CC, et al. Scrub typhus complicated by intracranial hemorrhage—A case report. Tzu Chi Med J. 2005;17:111–4.
9. Kim DE, Lee SH, Park KI, et al. Scrub typhus encephalomyelitis with prominent neurological signs. Arch Neurol. 2000;57(12):1770–2.
10. Kang JI, Kim DM, Lee J. Acute sensorineural hearing loss and severe otalgia due to scrub typhus. BMC Infect Dis. 2009;9:173.
11. Misra UK, Kalita J, Mani VE. Neurological manifestations of scrub typhus. J Neurol Neurosurg Psychiatry. 2015;86(7):761–6.
12. Remalayam B, Viswanathan S, Muthu V, et al. Altered sensorium in scrub typhus. J Postgrad Med. 2011;57(3):262–3.
13. Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. J Infect. 1996;33(3):185–91.
14. Blacksell SD, Bryant NJ, Paris DH, et al. Scrub typhus serologic testing with the indirect immunofluorescence method as a diagnostic gold standard: a lack of consensus leads to a lot of confusion. Clin Infect Dis. 2007;44(3):391–401.
15. Sun Q, Sha W, Xiao HP, et al. Evaluation of Cerebrospinal Fluid Adenosine Deaminase Activity for the Differential Diagnosis of Tuberculous and Nontuberculous Meningitis. Am J Med Sci. 2012;344(2):116–21.

Rationale for Procalcitonin in the Intensive Care Unit

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INTRODUCTION

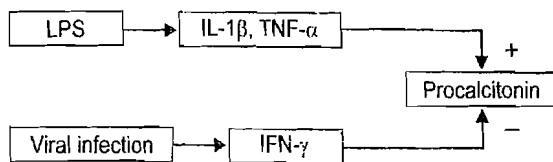
Early correct diagnosis of sepsis is crucial in improving patient outcomes. On one hand, initiation of appropriate antibiotic therapy improves survival in septic shock while unwarranted initiation of antibiotic therapy can lead to increased cost and increasing antibiotic resistance. As much as the above two principles are clear and widely accepted, in reality, often the presentation of illnesses are nonspecific and there exists a significant overlap between bacterial sepsis and other inflammatory states that closely mimic it (e.g., viral syndromes, autoimmune syndromes, allograft rejection, pancreatitis, etc.). The new sepsis definition recognizes this fallacy and hence, has gone away from using the systemic inflammatory response syndrome (SIRS) as a screen for sepsis.¹ It is in these situations, clinicians are faced with the dilemma of whether to initiate antibiotics or not and hence, usually err on the side of early initiation. The other important decision in the early phase of management of sepsis is appropriate triage of patients, especially when organ dysfunction is absent or minimal at presentation. Finally, the duration of antibiotic therapy for most bacterial syndromes is arbitrary based on consensus guidelines rather than strong evidence base and deciding termination of antibiotic therapy in culture negative sepsis becomes challenging.

Despite the successful implementation of diagnostic biomarkers in different fields of medicine (for example, D-dimers in pulmonary embolism, natriuretic peptides in acute heart failure, troponin in myocardial infarction), accurate and timely diagnosis of bacterial infections still remains a challenge. The main disadvantages of many current diagnostic methods are delays (e.g., culture methods), suboptimal sensitivity (e.g., blood cultures), and low specificity due to contamination (e.g., sputum cultures). Although new polymerase chain reaction techniques have been evaluated for early and rapid diagnosis of certain bacterial infections, they are not widely available and are expensive at present. Inflammatory markers, such as

C-reactive protein (CRP) or leukocytosis, lack sensitivity and specificity for bacterial infections. An ideal biomarker for sepsis, therefore, should be able to help rule in or rule out sepsis, in patient triage and prognostication, deciding the need for antibiotic therapy, and assist in following the clinical resolution, and therefore, the duration of antibiotic therapy.² Although several such biomarkers have been evaluated, none meet all the above criteria. The biomarker that has been most extensively evaluated, marketed, and that is most widely available for clinical use is procalcitonin (PCT). Hence, this chapter reviews the physiology of procalcitonin, the existing evidence, and its rationale, if any, for its use in the intensive care unit (ICU).

WHAT IS PROCALCITONIN?

Procalcitonin is a propeptide of calcitonin that is ubiquitously expressed as part of the host's inflammatory response to a variety of insults. Although calcitonin is a neurohormone classically produced in the C-cells of the thyroid gland and involved in calcium homeostasis, PCT is one of several calcitonin precursors involved in the immune response. Procalcitonin is raised in a variety of inflammatory states, including cardiogenic shock, trauma, necrotizing pancreatitis, burns, surgery, and infection. Procalcitonin in inflammatory states is secreted by non-neuroendocrine parenchymal cells throughout the body (e.g., lung, liver, kidney, fat, muscle, stomach), especially from the lungs and intestine. The cause for this secretion may be due to changes in the promoter for the PCT gene, responding to intestinal translocation of lipopolysaccharide or other bacterial constituents, or by a secondary proinflammatory cytokine stimulus such as tumor necrosis factor.³ Hyperprocalcitonemia in marked systemic inflammation or in infection occurs within 2–4 hours, often reaches high values in 8–24 hours, and then persists as long as the inflammatory process continues (i.e., days to weeks).⁴ With recovery, these levels normalize, predominantly being cleared by the parathyroid glands, with renal clearance being



LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

FIG. 1: Synthesis of procalcitonin

very minimal. Procalcitonin levels seem to correlate with the severity of bacterial infections and are unaffected by renal function or dialysis. Notably, viral infections may decrease the production of PCT due to the secretion of interferon- γ (Fig. 1).

CURRENT PROCALCITONIN ASSAYS

Although it would be highly desirable, there is no assay (research or otherwise) that detects the 116 kDa PCT peptide exclusively. Depending on the type of assay, all tests detect various portions of several calcitonin precursors. The assay utilized in the vast majority of studies is the immunoluminometric PCT assay (i.e., LUMitest), which detects the PCT prohormone and the conjoined segment of calcitonin and calcitonin-carboxyl-peptide.⁵ With this assay, values below 0.5 ng/mL are best referred to as indeterminate. Furthermore, because 0.5 ng/mL exceeds the average normal value by more than fivefold (normal value <0.1 ng/mL), many mild increases in PCT values are missed.

Procalcitonin has different diagnostic properties when compared with CRP or lactate which are often recommended for diagnosing sepsis. C-reactive protein, for example, has a low specificity for sepsis and concentrations do not indicate the risk and severity of sepsis well. It responds late and plasma levels may be altered by immunosuppression. Moreover, a decline of CRP towards the normal range may take from several days up to 1 week.

Lactate is primarily more a marker of cellular and oxidative metabolism than perfusion. Significantly increased or high levels of lactate mainly occur in patients with severe or progressive stages of sepsis, e.g., if severe organ dysfunction or septic shock are already present. Furthermore, lactate does not differentiate septic from nonseptic shock.

Due to the distinct profile of PCT as compared to these markers, PCT is commonly used in a number of ICUs as a biomarker of sepsis and its value incorporated into the diagnostic and therapeutic decisions.

PROCALCITONIN AS A DIAGNOSTIC BIOMARKER OF BACTERIAL SEPSIS

There have been a number of studies looking at the diagnostic ability of PCT in critically ill patients and, more specifically, its ability to differentiate between SIRS and bacterial sepsis. These studies are generally small, methodologically heterogeneous, and use different PCT cutoff points to define

normal.⁶ For example, in one study of 545 patients with community acquired pneumonia (CAP) in the emergency department setting, a PCT above 0.1 ng/mL had a 90% sensitivity and 59% specificity to predict bacterial pneumonia with an area under the curve of 0.88.⁷ However, in another study, optimal cutoff of PCT was noted to be 0.2–0.25 ng/mL with a much lower sensitivity and specificity.⁸ There have been many meta-analyses performed within the last 5 years, that have attempted to clarify this situation.

The latest from Hoeboer et al. included 58 of 1,567 eligible studies providing a total of 16,514 patients, of whom 3,420 suffered from bacteremia. In the overall analysis, the area under the receiver operating characteristic (ROC) curve was 0.79. The most widely used PCT cutoff value was 0.5 ng/mL with a corresponding sensitivity of 76% and specificity of 69%.⁹ They concluded that, PCT had a fair diagnostic accuracy for bacteremia in adult patients suspected of infection or sepsis. In particular, low PCT levels could be used to rule out the presence of bacteremia, however, its negative predictive value in patients without bacteremia remains unclear.

Procalcitonin has been evaluated to distinguish infected from noninfected patients in the postsurgical setting. While the PCT levels have been generally higher in infected than in noninfected patient, the optimal thresholds for this discrimination varied widely with suboptimal sensitivity and specificity.¹⁰ Moreover, PCT levels may not be elevated when infection is confined to one particular compartment (e.g., mediastinitis).¹¹ Use of PCT to differentiate infected pancreatic necrosis from noninfected necrosis has been extensively evaluated with a wide variability in the optimal cutoffs and sensitivity and specificity, thereby making PCT a test with poor clinical value to guide management.¹²

Similarly, several small studies that have evaluated the value of PCT in the early diagnosis of ventilator-associated pneumonia have revealed discouraging results.^{13,14} Procalcitonin value in diagnosing infection in immunocompromised host also seems very limited.¹⁵

The negative results of the studies evaluating the utility of a single PCT levels in diagnosing bacterial infections could be due to several factors, few are mentioned below:

- The timing of PCT measurement could impact its value in diagnosing bacterial infections. False-negative results can occur if samples are taken too early in the course of infection
- Procalcitonin can remain elevated several weeks after an infection and its diagnostic value in detection of a second new bacterial infection may be muted, especially in critically ill patients who often have recurrent infections
- When infection is confined within a compartment, serum PCT levels may not be very reflective.

Therefore, the diagnostic accuracy of a single PCT value as a biomarker to rule in or rule out an acute bacterial infection in the ICU remains inadequate.

Then, would serial serum PCT levels be a better way to pick up an infection? The sequential measurement of PCT in

identifying healthcare-associated infection is undoubtedly attractive, and there is some evidence that PCT measured on the day infection is suspected and twice or thrice weekly might be clinically useful. Procalcitonin, used in this way, may reduce unnecessary antibiotic prescribing in patients who deteriorate for noninfectious reasons, but it will also add to healthcare costs. The practicality and the cost-effectiveness of such a strategy in a resource limited setting, such as ours, makes serial PCT measurements a nonviable method to diagnose and guide antibiotic therapy, and hence, cannot be recommended based on current evidence.

ROLE OF PROCALCITONIN IN ANTIBIOTIC INITIATION

Since PCT levels seem to be elevated in bacterial sepsis, the logical question has been whether admission PCT value could be used to determine the need for antibiotic therapy or not. In the emergency department setting, algorithms that incorporated initial PCT levels to decide antibiotic initiation have shown a reduction in antibiotic consumption in patients with CAP, but did not impact hospital survival.¹⁶

The largest randomized controlled trial (RCT) that has evaluated the usefulness of PCT in guiding antibiotic therapy in the ICU setting is the PRORATA (Use of Procalcitonin to Reduce Patients' Exposure to Antibiotics in Intensive Care Units) trial. The PRORATA trial was a multicenter study which compared PCT guided antibiotic therapy (307 patients) to usual care (314 patients) with suspected bacterial sepsis on admission to the ICU. Though the recommendations were not followed in 71% of patients in the PCT group, overall the PCT group had significantly more days without antibiotic exposure and received significantly fewer days of antibiotics. Antibiotics were prescribed in 21% patients despite an initial serum PCT below 0.5 ng/mL on admission. Importantly, there was no difference between the PCT guided and control groups in the initial antibiotic prescription rates.¹⁷ Another smaller study also found no difference in the antibiotic prescription rates between PCT guided and the control group in ICU patients with bacterial infections.¹⁸ In both the above studies, a significant proportion of patients received antibiotic therapy despite initial PCT level below 0.5 ng/mL. This underlines the important fact that physicians are reluctant to base their decision to initiate antibiotic therapy based on a PCT level which in turn could be related to the physicians' eagerness to start antibiotics early to improve survival and the lack of sensitivity of a single PCT value in diagnosing early infection.

In another randomized controlled study, role of PCT kinetics in guiding antibiotic escalation was evaluated in 1,200 ICU patients.¹⁹ In the Procalcitonin and Survival Study (PASS) trial, patients were randomized to standard antibiotic guidance or PCT guided antibiotic escalation. Serum PCT was measured daily after the onset of infection and absolute PCT value above 1 ng/mL or below 10% reduction from the

previous day were considered "alert PCT" values. Clinicians were suggested to obtain infection specific cultures or diagnostic imaging on days with "alert PCT" values and were encouraged to follow an antibiotic escalation algorithm. The study could not demonstrate any significant differences in the 28-day survival between the groups, but the PCT group consumed more antibiotics and had longer days on mechanical ventilation and ICU length of stay.

PROCALCITONIN AS A PROGNOSTIC MARKER IN BACTERIAL SEPSIS

Few studies have looked into the role of PCT as a prognostic marker in severe sepsis. Giamarellos-Bourboulis et al. found that PCT levels on day 1 could predict the types of organ dysfunction in patients who eventually progressed to multiple organ dysfunction syndrome.²⁰ Another study by Min-Yi Huang et al. found that the prognosis of patients with severe sepsis and septic shock may be associated with dynamic changes of PCT at 48 and 96 hours after admission to the ICU. They concluded that serial changes in PCT could assist physicians in the risk stratification of critically ill patients with severe sepsis and septic shock.²¹ Although some promising studies encourage the use of PCT as a marker for sepsis outcome, more studies are needed in order to confirm this finding.

UTILITY OF PROCALCITONIN KINETICS IN STOPPING OR DE-ESCALATING ANTIBIOTICS

The use of PCT as an antimicrobial stewardship tool is extremely attractive in the current climate of increasing antibiotic resistance. Procalcitonin variation after starting antibiotics may be closely associated with outcome than the initial crude PCT. Therefore, a decrease in serum PCT has been proposed as a guide to stop/deescalate antibiotics. Several small RCTs have demonstrated significant decreases in antibiotic use without any apparent increase in harm in various bacterial infections.²²⁻²⁵

In the PRORATA study, 621 patients were randomized to either PCT guided antibiotic initiation and deescalation or standard antibiotic management. Although there were no differences in the antibiotic initiation rates between the two groups, patients in the PCT group had on an average of 2.7 days less on antibiotics compared to the control group with no difference in the mortality between the two groups.¹⁷ One meta-analysis also revealed lower duration of antibiotic with PCT guided antibiotic therapy compared to standard care with no particular differences in relapse or persistent infections and mortality.²⁶

Although PCT guidance in addition to clinical course may serve as a useful guide to stop/deescalate antibiotics, its cost-effectiveness in resource limited setups needs to be explored more. It may be worthwhile looking at PCT guided termination or deescalation of antibiotics in culture negative

sepsis which may contribute up to one-third of septic patients in the ICU.

CONCLUSION

In the diagnosis and prognosis of sepsis in critically ill patients, PCT is an improvement on CRP and other traditional markers; however based on current evidence, it lacks the necessary accuracy to distinguish sepsis from other inflammatory states or to serve as a guide for antibiotic initiation. At present, a single value of PCT cannot be used to confidently rule in or rule out an infection. There is stronger evidence for its use as a tool to reduce antibiotic therapy duration and it is perhaps in this role that its utility should be explored further. However, the cost-effectiveness of PCT as an antibiotic stewardship tool must be evaluated before recommending it for widespread use.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):801-10.
2. Vincent JL, Teixeira L. Sepsis Biomarkers. Value and Limitations. *Am J Respir Crit Care Med*. 2014;190(10):1081.
3. Domenech VS, Nylen ES, White JC, et al. Calcitonin gene-related peptide expression in sepsis: Postulation of microbial infection specific response elements within the calcitonin I gene promoter. *J Invest Med*. 2001;49:514-21.
4. Reinhart K, Karzai W, Meisner M, et al. Procalcitonin as a systemic inflammatory response to infection. *Intensive Care Med*. 2000;26:1193-200.
5. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med*. 2008;36(3):941-52.
6. Bréchet N, Hékimian G, Chastre J, et al. Procalcitonin to guide antibiotic therapy in the ICU. *Int J Antimicrob Agents*. 2015;46:S19-24.
7. Müller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis*. 2007;7(1):1.
8. de Kruif MD, Limper M, Gerritsen H, et al. Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. *Crit Care Med*. 2010;38(2):457-63.
9. Hoeboer SH, van der Geest PJ, Nieboer D, et al. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2015;21(5):474-81.
10. Sponholz C, Sakr Y, Reinhart K, et al. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10(5):1.
11. Aouifi A, Piriou V, Bastien O, et al. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. *Crit Care Med*. 2000;28(9):3171-6.
12. Mofidi R, Suttie SA, Patil PV, et al. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. *Surgery*. 2009;146(1):72-81.
13. Jung B, Embriaco N, Roux F, et al. Microbiological data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score. *Intensive Care Med*. 2010;36(5):790-8.
14. Pfister R, Kochanek M, Leygebe T, et al. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. *Crit Care*. 2014;18(2):1.
15. Bele N, Darmon M, Coquet I, et al. Diagnostic accuracy of procalcitonin in critically ill immunocompromised patients. *BMC Infect Dis*. 2011;11(1):1.
16. Schuetz P, Müller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;9:CD007498.
17. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *The Lancet*. 2010;375(9713):463-74.
18. Layios N, Lambermont B, Canivet JL, et al. Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. *Crit Care Med*. 2012;40(8):2304-9.
19. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med*. 2011;39(9):2048-58.
20. Giamarellos-Bourboulis EJ, Mega A, Grecka P, et al. Procalcitonin: a marker to clearly differentiate systemic inflammatory response syndrome and sepsis in the critically ill patient? *Intensive Care Med*. 2002;28(9):1351-6.
21. Huang MY, Chen CY, Chien JH, et al. Serum procalcitonin and procalcitonin clearance as a prognostic biomarker in patients with severe sepsis and septic shock. *Biomed Res Int*. 2016;2016:1758501.
22. Stolz D, Smyrniotis N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Resp J*. 2009;34(6):1364-75.
23. Nobre V, Harbarth S, Graf J, et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med*. 2008;177(5):498.
24. Hochreiter M, Köhler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care*. 2009;13(3):1.
25. Schroeder S, Hochreiter M, Köhler T, et al. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. *Langenbeck's Arch Surg*. 2009;394(2):221-6.
26. Kopterides P, Siempos II, Tsangaris I, et al. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med*. 2010;38(11):2229-41.

Aerosolized Antibiotic

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INTRODUCTION

Ventilator-associated pneumonia (VAP) remains one of the most common intensive care unit (ICU)-acquired infections and is associated with greater ICU length-of-stay, mortality, and healthcare costs.^{1,2} Cases of late-onset VAP (occurring 5 days after initiation of mechanical ventilation) are more likely to be caused by multidrug-resistant (MDR) isolates such as the "ESKAPE" species (in particular *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), which adds to the increasing difficulty of treating VAP and correlates with high incidence of morbidity and mortality.¹ Current antibiotic treatments for VAP are typically given through the intravenous route. However, despite widespread implementation of current antibiotic guidelines for the treatment of pneumonia, clinical cure rates rarely exceed 60%, and recurrence rates remain high.² Aerosolized antibiotics could represent an attractive adjunct or alternative to intravenous antibiotics with numerous potential advantages. Reaching the deep lung through the tracheobronchial tree should allow a better control of the main source of parenchymal infection, i.e., bronchial colonization.³

Aerosolized antibiotics were first introduced in the 1970s as a form of prophylaxis for VAP, now, more than 30 years later, there is a resurgence of interest in using this mode of delivery as a primary or adjunctive treatment for ventilator-associated tracheobronchitis (VAT) or VAP. There are new data emerging that suggest these agents may effectively treat these pathogens when used in targeted and time-limited protocols.⁴ Aerosolized antibiotics provide high levels of drug in the lung and reduce the systemic toxicity associated with intravenous antibiotics.

EFFECTIVENESS OF ANTIBIOTICS AT THE SITE OF INFECTION

Ideally, antibiotic should attain concentration four times the minimum inhibitory concentration (MIC) against the

infecting pathogen at the site of infection. Fluoroquinolones like moxifloxacin penetrate well into lung tissue when administered intravenously,⁵ but many other antibiotics like β -lactam, aminoglycoside, glycopeptides (vancomycin), and polymyxins penetrate poorly in the lung tissue and are present in low concentration in epithelial-lining fluid (ELF).⁶⁻⁸ Moreover, the drug pharmacokinetics like increase volume of distribution, increase clearance of drug due to glomerular hyperfiltration, etc. may further decrease effectiveness of intravenous antibiotic.⁹ In these circumstances, especially in mechanically ventilated patients with pneumonia, aerosolized antibiotic may reach high concentration at the site of infection, while minimizing systemic side effects.^{10,11}

BENEFITS OF NEBULIZED ANTIBIOTICS

Earlier use of aerosolized antibiotic was limited due to lack of specific formulation for such use and technical limitation of delivering optimally the aerosolized drug particles to the lung parenchyma.^{12,13} Recent advances in the drug delivery systems and aerosol drug formulations have circumvented these earlier problems.

High Drug Concentrations in the Lung

Achieving a high concentration of effective drug much higher than MIC of infecting pathogen at the site of infection is the single most advantage of aerosolized antibiotic.^{14,15} This property has been demonstrated for most Gram-negative organisms in animal studies.^{16,17}

Both inhaled tobramycin and amikacin can achieve high-bronchial concentrations far in excess of the MICs for Gram-negative strains usually responsible for pneumonia.^{18,19} These concentrations may also exceed the MICs for MDR pathogen.

Low Systemic Exposure

Another advantage of aerosolized antibiotic with significant toxicity is the low-systemic exposure,²⁰ indeed, administering

antibiotics such as aminoglycosides by aerosolization generates significantly lower peak serum concentrations compared with intravenous administration.^{21,22} This leads to decrease organ toxicity like nephrotoxicity of aminoglycosides and colistin.²¹ It has been shown that suboptimal dose of systemic antibiotic may lead to mutant selection, thereby increasing antibiotic resistance and aerosolized antibiotics tend to avoid this phenomenon.^{23,24}

Reduced Need for Systemic Antibiotics

Any maneuver that decreases the overall use of systemic antibiotics result in decrease antibiotic resistance pressure and is an essential ingredient of antibiotic stewardship program as was evident in a phase II study.²⁵⁻²⁷

Characteristics of an "Ideal"-inhaled Antibiotic

- Suitable formulation for aerosolization
- Delivers high-antibiotic concentrations to the site of infection via an efficient device
- Limited-systemic penetration.

Ideal Antibiotic Formulation for Aerosolization (Fig. 1)

- Sterile, preservative-free and nonpyrogenic
- pH (4.0–8.0)
- Osmolarity (150–1,200 mOsm/L)^{12,15,21}

DELIVERY DEVICES²⁸⁻³¹

Commonly used nebulizers used with bronchodilator drugs are designed to deliver drugs to the airway, not the lung parenchyma. Deposition location is a function of particle size, usually expressed as mass median aerodynamic diameter

(MMAD). Typical jet nebulizers have a particle size of about 5 micron MMAD to optimize airway deposition. Whereas, an aerosolized particle size of 3 micron MMAD is required for deposition at lung parenchyma, which cannot be generated by available jet nebulizer. An additional factor of poor lung deposition of aerosolized particles in mechanically ventilated patient is the presence of humidity in the ventilator circuit, which can cause hygroscopic growth, increasing the particle size and a rainout effect in the endotracheal tube.³²

The main two types of devices are the jet nebulizers and ultrasonic nebulizers. Various commercially available nebulizers are designed to deliver a MMAD between 1 and 5 μ and they vary in their ability to generate optimum particle size with as much as a tenfold difference in the amount of drug delivered. Factors that predominantly influence drug delivery are aerosol particle size, composition of inhaled gas, and presence of lung disease.²³ Eisenberg et al. compared three different nebulizers (1 ultrasonic and 2 jet nebulizers) and found therapeutic levels in more than 90% of the patients for all nebulizers.³³ Minimal systemic drug levels were found in all patients. Certain variables in the delivery system were noticed by Miller et al. They noted that humidifying the air decreases the amount of drug delivery as the droplets clumped together and more readily attached to the wall of the tubing.³² A higher antibiotic delivery to the lung was noted with breath-actuated nebulization than continuous nebulization.³²

The need for improved delivery has led to the development of two devices. The Nektar Bayer Pulmonary Drug Delivery System (PDDS) is a single-use nebulizer inserted distal to the ventilator wye. A ceramic vibrating plate nebulizer delivers drug during inspiration (Box 1). The nebulizer is triggered by a separate airway pressure-sensing device. The reported particle size is 4.7 micron MMAD, and the humidity is turned off. The PARI Investigational eFlow Inline Nebulizer System (PARI) is a multiple-use, single-patient device that is placed on the inspiratory limb of the ventilator circuit. A stainless steel vibrating plate nebulizer is placed in a coaxial position to the ventilator air flow and is run continuously. Against conventional wisdom, the humidity is left on, but the initial particle size is about 2.8 micron, growing to 3.2 micron with humidity, so particles are small enough to avoid the rainout effect.³⁴

AEROSOLIZED ANTIBIOTICS IN CRITICALLY ILL VENTILATED PATIENTS

Aerosolized antibiotics have been used to prevent infection as well as in treatment protocols.

Prophylaxis

Prophylactic use of aerosolized antibiotic to prevent VAP is not well supported in the literature. A recent meta-analysis by Falagas et al.³⁵ of 12 prophylactic trials of which only 8 were

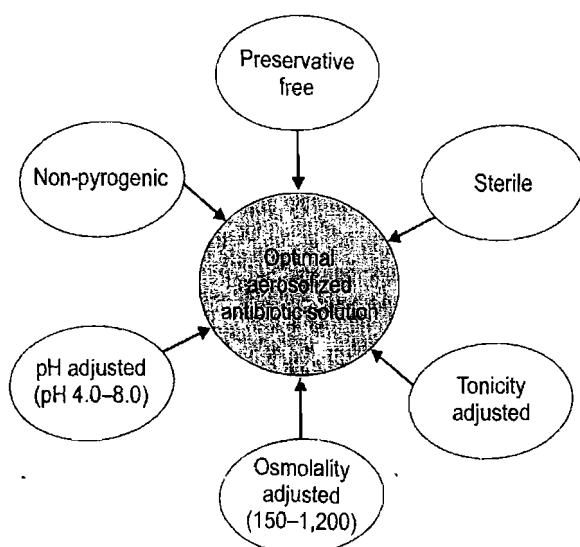


FIG.1: Ideal properties of an antibiotic solution for aerosolization

Box 1: Optimal technique for drug delivery via jet nebulizer in ventilated patients

- Review order, identify patient and assess need for bronchodilator
- Suction endotracheal and airway secretions
- Place drug in nebulizer to fill volume of 4–6 mL
- Place nebulizer in the inspiratory line 46 cm from the patient Y connector
- Turn off flow-by or continuous flow during nebulizer operation
- Remove HME (heat-and-moisture exchanger) from circuit
- Set gas flow to nebulizer at 6–8 L/min:
 - Use a ventilator, if it meets the nebulizer flow requirements and cycles on inspiration
 - Use continuous flow from external source
- Adjust ventilator volume or pressure limit to compensate for added flow
- Tap nebulizer periodically and until nebulizer begins to sputter
- Remove nebulizer from circuit, rinse with sterile water and dry, and store in safe place
- Reconnect humidifier or HME, return ventilator settings and alarms to previous values
- Monitor patient for adverse response.
- Assess outcome and document findings

either randomized-controlled trials (RCTs) or prospective comparative trials. Incidence of VAP and all-cause mortality was the primary outcome of interest. Colonization with *P. aeruginosa* was the secondary outcome. Analysis of these trials showed decreased incidence of VAP and decreased incidence of pseudomonas colonization but no change in mortality.

Current guidelines from both the Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) do not recommend this therapy in the absence of benefit in hard endpoints like mortality.³⁶ Aerosolized antibiotics have also been evaluated as prophylaxis for VAP in few more studies. A meta-analysis of five RCTs involving about 400 patients demonstrated a reduction in the risk of VAP for patients assigned to nebulized antibiotics compared with placebo, but no reduction in mortality was observed.³⁵

Nebulized antibiotics for VAP prophylaxis were not recommended in the 2005 ATS/Infectious Diseases Society of America consensus document due to concerns about the promotion of antibiotic resistance and the design limitations of published RCTs.^{36–38}

Cystic Fibrosis^{39,33}

As reviewed by the European Cystic Fibrosis (CF) Society Consensus Group,⁴⁰ the earliest studies of inhaled antibiotics in CF focused on inhaled aminoglycosides—specifically, tobramycin, gentamicin, and amikacin. Aminoglycosides were chosen because of their limited absorption across epithelia permitting high concentrations at the site of

infection and minimizing systemic toxicity. Based on the landmark studies conducted on tobramycin inhalation solution mentioned above, clinical guidelines for chronic stable CF lung disease continue to note a high level of evidence supporting the use of inhaled tobramycin in chronic *P. aeruginosa* infection in both the United States and Europe.^{41–43}

Non-cystic Fibrosis Bronchiectasis

Tobramycin solution for inhalation was examined in a placebo-controlled, double blind, randomized study of 74 patients with bronchiectasis and grossly purulent sputum-containing *P. aeruginosa*.⁴⁴ Over the 4-week treatment period, there was a significant reduction in sputum *P. aeruginosa* density (one-thirds eradicated *P. aeruginosa*), but no improvement in lung function was observed, and tobramycin-treated patients were more likely to report an increase in cough, wheezing and dyspnea. A subsequent crossover RCT of tobramycin solution for inhalation in 30 patients with non-CF bronchiectasis and *P. aeruginosa* treated over a longer period of 6 months demonstrated a reduction in the number of more severe exacerbations requiring hospitalization but no significant change in the overall number of exacerbations, pulmonary function or quality-of-life.⁴⁵ These two small studies examining tobramycin formed the basis for the 2010 British Thoracic Society non-CF bronchiectasis guidelines, which provided a level-C recommendation for the use of long-term nebulized antibiotics in non-CF bronchiectasis.⁴⁶ However, the guidelines mention that patients could be considered for long-term nebulized antibiotics, if they are chronically colonized by *P. aeruginosa*, and they experienced three or more exacerbations per year that caused significant morbidity.

Ventilator-associated Pneumonia (Table 1)

Aerosolized antibiotics have been studied as alternative or adjunctive agents to intravenous antibiotics in patients with VAP caused by Gram-negative bacteria.⁴⁷ The initial motivation for exploring inhaled antibiotics in these settings were the high rates of treatment failure reported when intravenous aminoglycosides were used alone or in combination with other intravenous antibiotics to treat drug-resistant Gram-negative bacteria in intubated patients and patients with tracheostomy.⁴⁸

Based on the consensus guidelines created by a joint committee of the American Thoracic Society and Infectious Diseases Society of America in 2005, aerosolized antibiotics were not considered valuable in the treatment of VAP but “could be considered as adjunctive therapy in patients with MDR Gram-negatives who are not responding to systemic therapy.”³⁷ Since this document was published, there have been two RCTs investigating nebulized antibiotics as alternative or adjunctive agents to IV antibiotics in VAP,

TABLE 1 Clinical trials of aerosolized antibiotics in patients with ventilator-associated pneumonia

Reference	Design	Number of patients	Treatment	Outcomes (aerosol vs. control)
Arnold et al. ²¹	Retrospective, single-center, cohort	93	Adjunct aerosolized colistin or tobramycin vs. intravenous antibiotics	30-day mortality: 0 vs. 18%
Lu et al. ²²	Prospective, randomized	40	Aerosolized ceftazidime and amikacin vs. intravenous ceftazidime and amikacin	Success: 70 vs. 55%; superinfection: 15 vs. 15%; day-28 mortality: 10 vs. 5%
Lu et al. ¹¹	Prospective, observational, comparative (not randomized)	165	Aerosolized colistin IV aminoglycosides vs. IV β -lactams plus aminoglycosides or quinolones	Clinical cure: 67 vs. 66%; superinfection: 6 vs. 13%; mortality: 16 vs. 23%
Niederman et al. ²⁶	Double-blind, randomized	69	Aerosolized amikacin (q12 h, q24 h) or placebo, each with IV antibiotics	Target concentration: 50 vs. 17%; clinical cure: 94 vs. 75 vs. 88%
Montgomery et al. ³⁴	Double-blind, randomized, phase 1	4	Escalating doses of aerosolized amikacin and fosfomycin	Amikacin: 98-fold higher than <i>P. aeruginosa</i> MIC ₉₀ ; fosfomycin: 68-fold higher than MRSA MIC ₉₀

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

and both have demonstrated favorable microbiologic responses but no impact on other clinical or radiographic outcomes.^{22,49}

Are Aerosolized Antibiotics Useful in Treating Ventilator-associated Tracheobronchitis and/or Ventilator-associated Pneumonia?

Meta-analyses of five RCTs that compared topical administration (aerosolization or instillation) with or without concurrent usage of systemic antibiotics with control treatment.⁴⁷ Patients receiving aerosolized antibiotics had less VAP (clinical diagnosis), odds ratio (OR) 2.39 [95% confidence interval (CI) 1.29–4.44]. Mortality, microbiological cure, and toxicity were similar in two arms. *Pseudomonas* and *Acinetobacter* species infections, which are one of the most resistant bacteria encountered in the ICU, were studied in a few recent trials.^{50–54} These bacteria are usually MDR due to their property of producing both extended spectrum-beta-lactamases and metallo-lactamases and they are often sensitive only to polymyxin.⁵⁵ Aerosolized colistin along with systemic antibiotic in lung infections by these two organisms had shown good clinical response in a study by Kwa et al.⁵¹ There have been two randomized placebo-controlled studies with important positive clinical outcomes.^{56–58} In a double-blind, placebo-controlled study of aerosolized amikacin delivered via vibrating mesh technology, the PDDS was given as an adjunctive therapy in ventilated patients with Gram-negative pneumonia.⁵⁶ The aerosolized group needed much less systemic antibiotic than the placebo group. Initial data for the treatment of methicillin-resistant *S. aureus* (MRSA) via aerosolized vancomycin in ventilated patients was also provided in this study. Ventilator-associated tracheobronchitis and VAP secondary to MRSA had no improvement in the placebo arm. Three patients with MRSA

and VAT received aerosolized vancomycin. Two of these did not have VAP at randomization and remained free of VAP at the end of treatment. The one patient who had MRSA and had VAP had clinical resolution at end of aerosolized vancomycin treatment as well as eradication of the MRSA.

Post-lung Transplantation

Inhaled antibiotics have been used off-label to prevent and treat bacterial and fungal infections after lung transplantation over the past few decades, but rigorous RCTs evaluating their use post-lung transplant have not been conducted. As a prophylactic measure to prevent allograft Gram-negative bacterial infections, inhaled aminoglycosides and colistin have been used as adjunctive agents to intravenous antibiotics in patients with CF post-transplant, especially in patients who have a history of pretransplant colonization with MDR Gram-negative organisms such as *P. aeruginosa* or *Burkholderia cepacia*.⁵⁹ Lung transplant recipients have higher rates of invasive *Aspergillus* infections compared with other solid organ transplant recipients due to more intense immunosuppression and altered mucociliary clearance.^{60,61} Nebulized amphotericin B has been investigated as antifungal prophylaxis in a few nonrandomized, comparative studies.^{62–64} In two separate studies, nebulized liposomal amphotericin B was compared with nonliposomal amphotericin B deoxycholate. In both studies, rates of invasive *Aspergillus* infections were low and comparable between the two treatment groups, but the liposomal form was better tolerated.^{62,63}

Mycobacterial Infections

No RCTs have investigated inhaled antibiotics in patients with tuberculous (TB) or nontuberculous mycobacterial

(NTM) lung disease to date, but this remains a very active area of research.^{65,66} Inhaled antitubercular antibiotics have the potential to be used as adjunctive agents to conventional systemic therapy to augment therapeutic drug levels or as part of second-line anti-TB regimens. Mycobacteria are prototypic intracellular pathogens that reside within alveolar macrophages. A potential advantage of inhaled antibiotics in this setting is that drug particles can be phagocytosed by alveolar macrophages within the airways and alveoli, resulting in higher drug concentrations within the macrophage cytosol than would otherwise be achieved using systemic agents, and potentially overcoming drug resistance.⁶⁵ For NTM lung disease, nebulized nonliposomal amikacin was added to standard therapy in a nonrandomized and uncontrolled study of 20 patients with treatment-refractory NTM disease, which resulted in improved symptoms and microbiologic outcomes, but one-third of patients had to stop treatment due to toxicity.⁶⁷

Chronic Obstructive Pulmonary Disease

There are no published RCTs examining the effects of inhaled antibiotics on health outcomes in chronic obstructive pulmonary disease. In a small and uncontrolled study of patients with severe chronic obstructive pulmonary disease and colonization with MDR *P. aeruginosa*, tobramycin solution for inhalation was administered at a dose of 300 mg twice daily for 14 days.⁶⁸ There was a significant reduction in sputum inflammatory mediators at the end of the 2-week treatment period and a 42% reduction in the incidence of acute exacerbations in the 6 months post-treatment, when compared with the 6 months pretreatment. With these limited data, it is not possible to assess efficacy or safety of inhaled antibiotics in this population.

AEROSOLIZED ANTIBIOTIC DOSING^{69,70}

Aerosolized antibiotic dosing is given in table 2.

TABLE 2 Aerosolized antibiotic dosing

Study	Type of study	Number of patients	Age (Y)	Major characteristics	Dose nebulized	Duration
Palmer et al. ¹³	Double-blind, randomized, placebo-controlled	43	19–92	ICU, MV	Vanc 120 mg/2 mL q8 Gent 80 mg/2 mL q8	Maximum 14 days
Palmer et al. ²⁵	Prospective, serial study, self-controlled	6	19–96	ICU, MV	Gent 80 mg q8 Amikacin 400 mg q8 Amikacin 400 mg q12 (renal failure)	2–3 weeks
Mohr et al. ²⁸	Retrospective chart review	22	21–78	ICU, MV	Tobra 300 mg q12 Amikacin 400 mg q8 Amikacin 400 mg q12 Amikacin 1 gram q12	7–10 days
Davis et al. ²⁹	Prospective open-label study	6	52–73	MAC treatment	Amikacin 15 mg/kg/day	4–52 months
Hallal et al. ²³	Randomized, double-blind, double-dummy	10	23–72	ICU, MV, GN VAP	Tobra 300 mg q12	14 days
Labiris et al. ³³	Labiris et al.	10	52 ± 21	CF or bronchiectasis	Gent 160 mg × 1	Single dose trial
Levine et al. ³⁰	Prospective, randomized	30	34	Burn patients with inhalation injury	Gent 80 mg q8	10 days
Dhand ⁵⁷	Review article	N/A	N/A	N/A	Colistin 40 mg q12 Colistin 80 mg q12 Colistin 160 mg q8 Tobra 300 mg q12	Not provided
Hamer ³⁹	Case series	3	45–67	ICU, pneumonia	Colistin 150 mg q12 Colistin 100 mg q12	11–14 days
Holloway et al. ³¹	Retrospective chart review	2	15–77	ICU, GN VAP	Colistin 160 mg	Not provided
Kwa et al. ³⁷	Retrospective chart review	21	61	ICU, MDR VAP	Colistin 80 mg q6–12	14 days (2–36 days)
Michalopoulos et al. ⁶⁹	Retrospective chart review	8	60 years	MDR VAP	Colistin 40 mg q6–8 Colistin 80 mg q8 Colistin 120 mg q8 Colistin 160 mg q8	3–19 days

CF, cystic fibrosis; GN, Gram-negative; ICU, intensive care unit; MAC, *Mycoplasma pneumoniae*; MDR, multidrug resistant; MV, mechanical ventilation; VAP, ventilator-associated pneumonia; gent, gentamicin; vanc, vancomycin; tobra, tobramycin.

CONCLUSION

Aerosolized antibiotic therapy may provide an efficacious means of treating respiratory tract infection when targeted at mechanically ventilated patients with proximal airway infection, VAT (with or without VAP) and with highly resistant organisms. The increasing prevalence and complexity of MDR organisms in nosocomial infections have fueled interest in novel therapeutic approaches. Adjunctive-aerosolized antibiotic (AAA) therapy for pneumonia has gained popularity and supported by apparent advantages of higher pulmonary antibiotic concentrations and lower systemic exposure. Balanced by a paucity of high-level evidence, consensus statements recommend AAA therapy be considered in patients with MDR pathogens not responding to intravenous therapy. One should hit hard and hit high, but at the site (target) where it should hit.

REFERENCES

- Restrepo MI, Anzueto A, Johnson S, et al. Economic burden of ventilator-associated pneumonia based on total resource utilization. *Infect Control Hosp Epidemiol.* 2010;31:509-15.
- Bercault N, Boulain T. Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. *Respir Ther.* 2001;29:2303-9.
- Routby JJ, Bouhemad B; Nebulized Antibiotics Study Group. Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies. *Anesthesiology.* 2012;117:1364-80.
- Palmer LB. Aerosolized antibiotics in critically ill ventilated patients. *Curr Opin Crit Care.* 2009;15:413-18.
- Wise R, Honeybourne D. Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract. *Eur Respir J.* 1999;14:221-9.
- Honeybourne D. Antibiotic penetration into lung tissues. *Thorax.* 1994;49:104-6.
- Cruciana M, Gatti G, Lazzarini L, et al. Penetration of vancomycin into human lung tissue. *J Antimicrob Chemother.* 1996;38:865-9.
- Imberti R, Rusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate administration. *Chest.* 2010;138:1333-9.
- Smith B, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest.* 2012;141:1327-36.
- Palmer LB. Aerosolized antibiotics in the intensive care unit. *Clinics Chest Med.* 2011;32:559-74.
- Lu Q, Luo R, Bodin L, Yang J, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology.* 2012;117:1335-47.
- Le J, Neuhauser M, Brown J. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. *Pharmacotherapy.* 2010;30:562-84.
- Wood GC, Swanson JM. Aerosolized antibacterials for the prevention and treatment of hospital acquired pneumonia. *Drugs.* 2007;67:903-14.
- Luyt CE, Combes A, Nieszkowska A, et al. Aerosolized antibiotics to treat ventilator-associated pneumonia. *Curr Opin Infect Dis.* 2009;22:154-8.
- Abu-Salah T, Dhand R. Inhaled antibiotic therapy for ventilator-associated tracheobronchitis and ventilator-associated pneumonia: an update. *Adv Ther.* 2011;29:728-47.
- Goldstein I, Wallet F, Robert J, Becquemin MH, Marquette CH, Routby JJ. Lung tissue concentrations of nebulized amikacin, during mechanical ventilation in piglets with healthy lungs. *Am J Respir Crit Care Med.* 2002;165:171-5.
- Goldstein I, Wallet F, Nicolas-Robin A, et al. Lung deposition and efficiency of nebulized amikacin during *Escherichia coli* pneumonia in ventilated piglets. *Am J Respir Crit Care Med.* 2002;166:1375-81.
- Badia J, Soy D, Adrover M, Ferrer M, et al. Disposition of instilled versus nebulized tobramycin and imipenem in ventilated intensive care unit (ICU) patients. *J Antimicrob Chemother.* 2004;54:508-14.
- Luyt CE, Clavel M, Guntupalli K, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. *Crit Care.* 2009;13:R200.
- Cooney G, Lum B, Tomaselli M, et al. Absolute bioavailability and absorption characteristics of aerosolized tobramycin in adults with cystic fibrosis. *Clin Pharmacol.* 1994;34:255-9.
- Wood C. Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. *Exp Rev Anti-Infect Ther.* 2011;9:993-1000.
- Lu Q, Yang J, Liu Z, Gutierrez C, et al. Nebulized ceftazidime and amikacin in ventilator associated pneumonia caused by *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med.* 2011;184:106-15.
- Dhand R. The role of aerosolized antimicrobials in the treatment of ventilator-associated pneumonia. *Respir Care.* 2007;52:866-84.
- Drlica K, Zhao X. Mutant selection window hypothesis updated. *Clin Infect Dis.* 2007;44:681-8.
- Hagerman JK, Hancock KE, Klepser ME. Aerosolized antibiotics: a critical appraisal of their use. *Expert Opin Drug Deliv.* 2006;3:71-85.
- Niederman M, Chastre J, Corkery K, et al. BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. *Intensive Care Med.* 2012;38:263-71.
- Niederman M, Chastre J, Corkery K, et al. The Amikacin Study Group. NKTR-061 (inhaled amikacin) reduces intravenous antibiotic use in intubated mechanically ventilated patients during treatment of Gram-negative pneumonia. *ATS 18-23 May 2007, Poster A326.*
- Palmer LB, Smaldone GC, Simon SR, et al. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. *Crit Care Med.* 1998;26:31-9.
- Sexauer WP, Fiel SB. Aerosolized Antibiotics in Cystic Fibrosis. *Seminars Crit Care Med.* 24:717-26.
- Dalby RN, Tiano SL, Hickey AJ. Medical devices for the delivery of therapeutic aerosols to the lungs. In: Hickey AJ. (Eds). *Inhalation Aerosols: Physical And Biological Basis for Therapy.* New York: Marcel Dekker; 1996. Pp. 441-73.
- Phipps PR, Gonda I. Droplets produced by medical nebulizers: some factors affecting their size and solute concentration. *Chest.* 1990;97:1327-32.
- Miller DD, Amin MM, Palmer LB, et al. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med.* 2003;168:1205-9.
- Eisenberg J, Pepe M, Williams-Warren J, et al. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizers systems. *Aerosolized Tobramycin Study Group.* *Chest.* 1997;111:955-62.
- Montgomery AB, Vallance S, Abuan T, et al. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow Inline nebulizer system in mechanically ventilated patients (abstract 42767 and poster 42767). *Am J Respir Crit Care Med.* 2013;187:A3236.
- Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. *Crit Care.* 2006;10:R123.
- American Thoracic Society/Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388-416.
- Stapleton KW, Finlay WH. Determining solute concentration within aerosol droplets output by jet nebulizers. *J Aerosol Sci.* 1995;26:137-45.
- Klick JM, du Moulin GC, et al. Prevention of Gram-negative bacillary pneumonia using polymyxin aerosol as prophylaxis: II. Effect on the incidence of pneumonia in seriously ill patients. *J Clin Invest.* 1975;55:514-9.
- Rau-JL. Design principles of liquid nebulization devices currently in use. *Respir Care.* 2002;47:1257-78.
- Heijerman H, Westerman E, Conway S, et al. Consensus Working Group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros.* 2009;8:295-315.

41. D'oring G, Flume P, Heijerman H, et al. Consensus Study Group. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros*. 2012;11:461-79.
42. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic Fibrosis Foundation, Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176:957-69.
43. Mogayzel PJ Jr, Naureckas ET; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187:680-9.
44. Barker AF, Couch L, Fiel SB, Gotfried MH, et al. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med*. 2000;162:481-5.
45. Drobnic ME, Suñe' P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Ann Pharmacother*. 2005;39:39-44.
46. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax*. 2010;65:i1-58.
47. Ioannidou E, Siempos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. *J Antimicrob Chemother*. 2007;60:1216-26.
48. Smith CR, Baughman KL, Edwards CQ, et al. Controlled comparison of amikacin and gentamicin. *N Engl J Med*. 1977;296:349-53.
49. Rattanaumpawan P, Lorstuthitham J, Ungprasert P, et al. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria. *J Antimicrob Chemother*. 2010;65:2645-9.
50. Berlana D, Llop JM, Fort E, et al. Use of colistin in the treatment of multiple drug-resistant Gram-negative infections. *Am J Health Syst Pharm*. 2005;62:39-47.
51. Kwa AL, Loh C, Low JG, et al. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2005;41:754-7.
52. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. *Am J Respir Crit Care Med*. 2000;162:328-30.
53. Michalopoulos A, Fotakis D, Vartzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. *Respir Med*. 2008;102:407-12.
54. Falagas ME, Kasiakou SK, Tsiodras S, et al. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res*. 2006;4:138-46.
55. Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. *NEJM*. 2008;358:1271-81.
56. Niederman MS, Chastre J, Corkery K, et al. Inhaled amikacin reduces IV antibiotic use in intubated mechanically ventilated patients [abstract]. *Am J Respir Crit Care Med*. 2007;175:A326.
57. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med*. 2008;36:2008-13.
58. Palmer LB, Baram D, Gunther MS, et al. Aerosolized vancomycin for treatment of Gram-positive respiratory infection in mechanically ventilated patients. *Am J Respir Crit Care Med*. 2003;167:A604.
59. Suhling H, Rademacher J, Greer M, et al. Inhaled colistin following lung transplantation in colonised cystic fibrosis patients. *Eur Respir J*. 2013;42:542-4.
60. Silveira FP, Husain S. Fungal infections in lung transplant recipients. *Curr Opin Pulm Med*. 2008;14:211-8.
61. Minari A, Husni R, Avery RK, et al. The incidence of invasive *Aspergillus* among solid organ transplant recipients and implications for prophylaxis in lung transplants. *Transpl Infect Dis*. 2002;4:195-200.
62. Drew RH, Dodds Ashley E. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplantation. 2004;77:232-7.
63. Monforte V, Ussetti P, Gavalda J. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation. *J Heart Lung Transplant*. 2010;29:523-30.
64. Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. *Transplant Proc*. 1997;29:627-8.
65. Misra A, Hickey AJ, Rossi C, et al. Inhaled drug therapy for treatment of tuberculosis. *Tuberculosis (Edinb)*. 2011;91:71-81.
66. Philley JV, Griffith DE. Management of nontuberculous mycobacterial (NTM) lung disease. *Semin Respir Crit Care Med*. 2013;34:135-42.
67. Olivier K, Shaw P, Glaser T, et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. *Ann Am Thorac Soc*. 2014;11:30-5.
68. Dal Negro R, Micheletto C, Tognella S, et al. Tobramycin nebulizer solution in severe COPD patients colonized with *Pseudomonas aeruginosa*: effects on bronchial inflammation. *Adv Ther*. 2008;25:1019-30.
69. Niven RW. Atomization and nebulizers. In: Hickey AJ (Eds). *Inhalation Aerosols: Physical and Biological Basis for Therapy*. New York: Marcel Dekker; 1996. Pp. 273-312.
70. Fink J. Aerosol drug therapy. In: Wilkins RL, Stoller JK, Scanlan CL (Eds). *Egan's Fundamentals of Respiratory Care*, 8th edition. St. Louis: Mosby; 2003. pp. 761-800.

Rapid Diagnostic Tests for Bacterial or Fungal Identification in Intensive Care Unit

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INTRODUCTION

In an era of multidrug-resistance microorganisms, infections are the most common complication seen in intensive care unit (ICU) patients. Recent advances in critical care medicine have also resulted in a steep rise in the incidence of invasive fungal infections over the recent years.¹ Rapid diagnosis and the determination of antimicrobial resistance markers are of utmost importance. There are several advantages in making rapid diagnosis of an infectious disease. Along with better patient management, preventive measures can be initiated in a timely manner. Also, early and accurate diagnosis not only helps for prompt treatment but it also limits the spread of disease by implementing effective preventive and isolation measures.

SPECIMEN COLLECTION AND TRANSPORT

Preanalytical aspects, such as specimen collection and transport, are the most essential step in laboratory diagnosis. It is very important to collect the proper specimen using sterile equipment and containers to prevent contamination of sample by extraneous environmental sources and normal flora. Isolation of infectious agents from contaminated sites, such as stool, poses a great challenge, hence, inhibitory agents should be used to select them over normal flora. In samples such as urine, prompt inoculation is needed to prevent doubling and quadrupling of viable bacteria.

Besides collection, specimen transport is also a vital aspect. Transportation of the specimen in a timely manner and in an appropriate transport medium is important. Especially for molecular testing where specimens range from whole blood to plasma to body fluids, swabs and occasionally tissues, ideal transportation techniques are important to prevent degradation of nucleic acids or overgrowth by normal flora. Also, when anaerobes are suspected, maintenance of the redox potential with transport media as Stuart's medium along with rapid transport to the laboratory ensures the

isolation of suspected organisms. In ICU settings, where rapid diagnosis is required for critically ill patients, ideal type of specimen and prompt transport are of utmost importance.

More than 20% of all nosocomial infections are acquired in ICUs besides the fact that less than 10% of the total number of beds are occupied by ICUs in most hospitals.²⁻⁴ Clinically significant infections observed in ICUs are intravascular catheter-related blood stream infections (CRBSIs), pneumonia—both ventilator and nonventilator associated, catheter-associated urinary tract infections (UTIs), skin and soft tissue infections (SSTIs), viral infections, and tuberculosis. Also, as multidrug-resistant pathogens are more frequently isolated,^{5,6} these impede the initiation of appropriate antibiotic therapy resulting in increased mortality.^{7,8} Hence, a rapid etiological diagnosis is vital.

DIAGNOSIS OF CATHETER-RELATED BLOODSTREAM INFECTIONS

To define CRBSI for diagnosing and treating purpose, specific laboratory testing is required to identify catheter as a source of bloodstream infection.⁹

There are three approaches for diagnosis of CRBSI. First, differential paired quantitative blood cultures, second is semiquantitative cultures of exit site around the portal of entry and of catheter hubs, and third is differential time to positivity.^{10,11}

Differential-paired Quantitative Blood Cultures

For proven CRBSI, differential colony count $\geq 3:1$ CFU/mL of bacteria from the blood culture drawn from central line compared to blood culture drawn from peripheral line should be present. This approach showed sensitivity of 80% and specificity of 90-100%. However, the risk of contamination and the risk of exposure of laboratory technicians to blood remain limitations.¹²

Combined Exit-site and Hub Cultures

Exit-site cultures are collected from skin 2 cm surrounding the catheter insertion site and the various hubs. If the growth of <15 CFUs per plate of the same microorganism is obtained from both the cultures, then the catheter as a source of the bloodstream infection is ruled out.¹⁰ Gram staining of skin and hub swabs is helpful for the rapid diagnosis of CRBSI.¹³

Differential Time to Positivity

This is defined as ≥ 2 hours of difference in time to positivity of a central venous catheter blood culture and a peripheral blood culture.^{14,15} However, a continuous-monitoring automated blood culture system is required. Depending on the type of catheter whether short-term or long-term and the patient, the Differential Time to Positivity (DTTP) test showed a sensitivity of 86–93%, specificity of 87–92%, positive predictive value (PPV) of 85–88%, and negative predictive value (NPV) of 89–95%.^{16,17}

Comparison of these three approaches was reported by Bouza et al.¹⁸ This study indicated that DTTP had better sensitivity of 96.4% and NPV of 99.4% than paired blood cultures to detect catheter-tip colonization (71.4 and 95.6%) while all three methods showed a high NPV.

RAPID DIAGNOSIS OF BLOODSTREAM INFECTIONS

The diagnosis of bloodstream infections in ICU patients is a major challenge. In such situations, blood cultures are indicated in all infections. Although recovery of bacteria from blood during episodes of sepsis is not difficult, certain concepts need to be understood. Adequate skin preparation prior to venipuncture and minimum of 30–40 mL of blood in blood culture bottles. Studies have shown that 2–3 blood culture sets are adequate for detecting common pathogens. The recovery in the first culture is 80%, 88% in two cultures, and 99% in all three cultures.¹⁹ Blood cultures are the gold standard diagnostic procedure, however, are time-consuming and slow. Only detection of viable microorganisms is possible and even sensitivity is low for slow growing, intracellular and fastidious microorganisms. There are fully automated instruments available today for rapid and accurate identification as well as susceptibility testing by minimum inhibitory concentration.²⁰

In today's era, molecular techniques provide faster and sensitive results along with the direct identification of responsible pathogens.^{21–23} Also, they are highly sensitive to detect low pathogen numbers as in meningitis. Afshari et al.²⁴ discussed various molecular tests commercially available today. Despite the potentially high PPV, the NPV may be insufficient to exclude infection. At present, molecular tests are used to complement the results of culture, especially in serious clinical situations.²⁵

Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) is now replacing biochemical and gene-sequencing methods for organism identification because it is easily implemented, highly accurate, and fast.^{26–28} The entire procedure for identification from smear preparation to reporting of the final result is completed within 30 minutes. The MALDI-TOFMS (mass spectrometry) has been used in the direct detection of bacteria-causing meningitis from cerebrospinal fluids (CSFs),²⁹ for rapid identification of atypical, Gram-negative organisms, and respiratory tract pathogens, which chronically infect patients with cystic fibrosis³⁰ and for CRBSI.³¹

Recently, MALDI-TOF MS has also been used to detect resistance mechanisms. It could be used as a screening tool for differentiating vancomycin-resistant *Enterococcus faecium* strains from vancomycin-susceptible *E. faecium* strains.³² The production of β -lactamases can be detected by employing mass spectrometric β -lactamase assay. Also, evaluated for identification and differentiation of carbapenemase-producing clinical strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa* from metallo β -lactamase-producing strains³³ and for detection and carbapenemase production in anaerobic bacterium.³⁴ Hence, this process is rapid, sensitive, and economical in terms of both labor and costs involved.

RAPID DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Though the terminology for VAP has changed, in this article we will use the original term. Hospital-acquired pneumonia, which includes ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia, is one of the leading causes of infection and mortality in ICU.²⁸ In patients with suspected VAP, lower respiratory tract sample should be submitted for microscopy examination and culture.³⁵ Even culture samples should ideally be transferred to microbiology department within 30 minutes of collection to avoid delay in processing and bacterial overgrowth.^{36,37} If unavoidable, specimens should be stored in refrigerated or frozen for 24 hours.³⁸

- Gram stain: Immediate reporting of Gram stain result guides the clinicians to make decision whether to initiate or to limit antibiotic treatment until culture results become available. Data showed sensitivity of 57–95%, specificity of 48–87%, PPV of 47–78%, NPV of 69–96%, and accuracy of 60–88%.^{39–42} Guidelines recommend a Gram stain directly on the sample and its quantitative culture.⁴³ Quantifying the proportion of cells-containing intracellular organisms in bronchoalveolar lavage (BAL) has also been proposed as a rapid method with high PPV.⁴⁴ Also, Gram stain does not seem to be affected by antibiotic therapy up to 72 hours prior to sampling.⁴⁵
- Serology: C-reactive protein (CRP) is a nonspecific biomarker of inflammation and may also be elevated in

the presence of pulmonary infiltrates of noninfectious cause.⁴⁶ Procalcitonin (PCT) too is not a good marker for the diagnosis of VAP.⁴⁷ However, in VAP, elevated levels indicate more severe clinical course and sustained high levels indicate worse outcome during the first week of illness.⁴⁸ Despite incompatibility, PCT seems to be a good indicator of bacterial load

- **Molecular method:** At present, there is no rapid procedure for the management of VAP. Molecular methods are still in development but such diagnostic assay should target various microorganisms and resistance genes, including most common pathogens like *Staphylococcus aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, and resistance genes like *mecA*, *bla_{KPC}*, *bla_{IMP}*, *bla_{VIM}*, and *bla_{OXA}*.⁴⁹

RAPID DIAGNOSIS OF URINARY TRACT INFECTION

Microbiological confirmation of a UTI is usually not as critical like sepsis. Gram staining from fresh uncentrifuged urine definitely shortens the turnaround time for reporting negative culture results and guides empirical antibiotic treatment. However, its use is limited because it needs more equipment and time than dipstick analysis and is unlikely to replace dipstick testing across all healthcare settings.⁵⁰ Gram staining has sensitivity of 82.2–97.9%; specificity 66.0–95.0%, PPV 31.6–94.3%, and NPV 95.2–99.5%.^{51–53}

Performing antimicrobial susceptibility testing directly from urine specimens has the advantage of next-day reporting. However, this method is condemned because the inoculum is not standardized and sometimes mixture of microorganisms found in the sample.^{54–57}

RAPID DIAGNOSIS OF SKIN AND SOFT TISSUE INFECTIONS

Usually, cultures are not indicated for uncomplicated SSTIs as they are treated in the outpatient setting.⁵⁸ However, cultures are indicated for patients who require operative incision and drainage because of the risk of deep structure and underlying tissue involvement.⁵⁹ Although sensitivity of blood cultures in cellulitis is low, it is beneficial for management of ICU patients. In emergency, Gram stain will help to determine the quality and potential pathogens present that must be followed by a conventional culture procedure.

OTHER RAPID MICROBIOLOGICAL TESTS USEFUL FOR INTENSIVE CARE UNIT PATIENTS

Detection of *Streptococcus pneumoniae* antigen and *Legionella pneumophila* serogroup 1 antigen in urine are most often used in for rapid diagnosis for patients with pneumonia.^{60,61} Another rapid tests used are for the detection

of viruses such as influenza, *Enterovirus*, central nervous system viruses and detection of *Mycobacterium tuberculosis* along with resistance genes.^{62,63}

Latex agglutination techniques are used to demonstrate the soluble polysaccharide antigens of *Neisseria meningitidis*, *Haemophilus influenzae* type B, and *S. pneumoniae* in patients of acute pyogenic meningitis. Especially in neonatal meningitis, detection of *Escherichia coli*, and group B streptococci can be done. These tests offer good specificity of more than 98% but the sensitivity varies with each bacterium tested. For *N. meningitidis* A, C, Y, W135, and *N. meningitidis* B or *E. coli* K1, it is 71 and 65%, respectively. For *S. pneumoniae*, it is 88 and 67% for *H. influenzae* and group B streptococci. This assay can also be used for serum after appropriate treatment with ethylenediaminetetraacetic acid.⁶⁴ Similarly, for detection of *L. pneumophila* serogroup 1 antigen in urine, an *in vitro* rapid immunochromatographic assay is available that has a clinical sensitivity and specificity of more than 95%.

BIOMARKERS IN SEPSIS

Many molecules had been studied so far as potential biological makers of sepsis. These molecules include CRP, PCT, pentraxin 3 (PTX3), soluble triggering receptor expressed on myeloid cells-1, soluble urokinase-type plasminogen receptor, proadrenomedullin, and presepsin.⁶⁵

C-reactive Protein

C-reactive protein is an acute phase protein synthesized by liver in response to inflammation or tissue insult and widely used as a marker to diagnose and manage patients with sepsis. In infection, CRP concentrations increased over time, yet remained unchanged in noninfected patients. Variation of at least 4.1 mg/dL in daily CRP monitoring was predictive of nosocomial infection with a sensitivity of 92% and specificity of 71%.⁶⁶ Study by Povoia et al. showed that in ICU patients, serum CRP of more than 8.7 mg/dL had sensitivity of 93% and specificity of 86%.⁶⁷ Similarly, if patients had CRP concentrations more than 10 mg/dL on ICU admission, a decrease in CRP after 48 hours showed mortality rate of 15%, while its increase was associated with a mortality rate of 61%.⁶⁸ Its low specificity is the primary drawback as a biomarker of sepsis in adults, still it is commonly used to screen for early onset sepsis in neonatology.⁶⁹

Procalcitonin

The peptide precursor of calcitonin is released by parenchymal cells, liver cells, kidney cells, adipocytes, and muscle cells in response to bacterial infections, leading to raised serum levels up to 5,000-fold within 2–4 hours and downregulated in patients with viral infections.⁷⁰ Thus, PCT is more specific than CRP for detecting bacterial infection.

Although, PCT has been shown to correlate with infection, it has some limitations. Accuracy of PCT to discriminate sepsis and systemic inflammatory response is low with sensitivity of 77% and specificity of 79%.⁷¹ It rises transiently in patients with nonseptic conditions and systemic inflammatory response syndromes, e.g., trauma, surgery, and heat stroke, and is not detectable in certain cases of sepsis.⁷²

Pentraxin 3

It is a protein with structural similarity to CRP, produced primarily by inflammatory cells rather than the liver. Like CRP, PTX3 has been shown to correlate with the severity of sepsis. However, it is also elevated in noninfectious inflammatory disorders, hence offers no advantage over CRP.⁷³

RECENT ADVANCES IN SYNDROMIC APPROACH OF INFECTIOUS DISEASES

Recently introduced FilmArray platform (BioFire) is a closed diagnostic system based on multiplex polymerase chain reaction (PCR) analysis with automated readout of results directly from CSF, respiratory sample, stool and positive blood cultures within 1 hour.

Blood Culture Identification Panel

This includes 19 bacteria, 5 yeasts, and 3 antibiotic resistance genes, could identify microorganisms with accuracy of 91.6% with monomicrobial growth.⁷⁴

Gastrointestinal Panel

This detects 22 different enteric pathogens with a good sensitivity of 100% and specificity more than 97.1% for all targets⁷⁵

Meningitis/Encephalitis Panel

This panel detects 14 targets with a specificity of 99.2% or greater for all analytes. The lower boundaries of the 95% confidence interval for specificity were 98.7% or greater for all targets.⁷⁶

Respiratory Panel

This panel that is currently for upper respiratory pathogens demonstrated very high-positive and negative percent agreement of 85–100% and 90–100%, respectively, for nearly all analytes.

RAPID DIAGNOSIS OF FUNGAL SEPSIS

Invasive fungal infections have dramatically increased in recent years and are associated with significant morbidity

and mortality. It is essential to have a high index of clinical suspicion and perform an early diagnosis for critically ill patients, including candidiasis, cryptococcosis, aspergillosis, and mucormycosis for successful outcome.

Microscopy

Gram stain is the most rapid and useful method in the diagnosis of infections and can be performed on any specimen. However, use of fluorescent stains such as calcofluor-white stain may enhance detection of hyphal filaments. India ink mount is useful to perform negative staining to detect capsular organisms, e.g., *Cryptococcus* in CSF.

Blood Culture

Sensitivity of blood cultures is only 55–70% (with three sets of blood culture and a total blood volume of 60 mL), therefore various nonculture methods are under development.⁷⁷

Serology

Many targets like mannan and antimannan antibodies (1,3)- β -D-glucan, enolase and antibodies to enolase and metabolic product D-arabinitol are being used. These tests may help in the pre-emptive antifungal therapy.

(1,3)-B-D-glucan

They have moderate sensitivity of 60–80% for candidemia and detection of serum. (1,3)-B-D-glucan is not very specific as false positive can occur due to dialysis, gauze, total parenteral nutrition, cardiopulmonary bypass, intravenous immunoglobulins, and other fungi like *Aspergillus*, *Fusarium*, *Trichosporon*, etc.⁷⁸

Galactomannan

Heat-stable heteropolysaccharide of the *Aspergillus* cell wall and a product of budding hyphae are useful for an early diagnosis and monitoring therapeutic response. The *Aspergillus* galactomannan (GM) enzyme immunoassay can be performed on serum, BAL, CSF, peritoneal fluid, and pericardial fluid. A positive result is considered as value of more than 0.5 for serum.⁷⁹ The specificity of GM is around 90–92%, hence good NPV.⁸⁰ In neutropenic patients, as the burden is high, serum GM has a very good sensitivity up to more than 90% and in non-neutropenic patients, it is around only 30% but BAL GM has a good sensitivity of more than 95%. False-positive results can occur in neonates and children with prior piperacillin-tazobactam and other β -lactams, cross-reactivity (*Bifidobacterium*, *Penicillium*, *Paecilomyces*, and *Histoplasma capsulatum*) and laboratory contamination.

Latex Agglutination Test

Latex agglutination test is a preferred test for rapid detection of *Cryptococcal* antigen. They can be used for diagnosis as well as therapeutic monitoring. The latex agglutination methods have a sensitivity of approximately 93% and specificity from 93-100% and are equivalent to enzyme-linked immunosorbent assay test in detecting antigen.⁸¹

Aspergillus Lateral Flow Device

Rapid immunochromatography test for qualitative detection of invasive pulmonary aspergillosis in human serum and BAL fluid. This test uses a monoclonal antibody JF5 that detects antigenic mannoproteins produced by the fungus during active growth. Results are obtained in <15 minutes with sensitivity of 81.8%, specificity of 84.7%, and NPV of 92.5%.⁸²

T2MR and T2Candida

T2MR is a magnetic resonance-based method that allows detection directly in complex samples, such as whole blood from patients suspected of sepsis, and T2Candida panel rapidly detects and identifies the causative pathogen of fungal sepsis directly from a patient's blood sample in a culture-independent manner with overall sensitivity of 91.1% and overall specificity of 99.4%.⁸³

Fungal Polymerase Chain Reaction

Fungal PCR is a new diagnostic tool for fungemia; however, many limitations like optimum specimen, deoxyribonucleic acid extraction, and contamination make them less cost effective. Matrix-assisted laser desorption-TOFMS is a reliable and time-saving approach for identification of various yeast species in bloodstream infections.⁸⁴

As the rapid diagnostic modalities for fungal infections are still under development, it is important to combine the knowledge of the risk factors, colonization status and molecular diagnosis for appropriate management. On the basis of these, empirical antifungal therapy can be started in critically ill patients with sepsis syndrome.

CONCLUSION

Significant advances have been achieved recently in rapid etiologic diagnosis of infectious diseases. Current diagnostics has shortened the turnaround times which is beneficial in treatment of many infections, such as sepsis, pneumonia, UTIs, SSTIs, viral infections, fungal infections, or tuberculosis. However, for better patient management, a dialogue between the clinician and laboratory physician regarding the diagnostics is imperative.

REFERENCES

1. Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med*. 2011;183(1):96-128.
2. Burgmann H, Hiesmayr JM, Savey A, et al. Impact of nosocomial infections on clinical outcome and resource consumption in critically ill patients. *Intensive Care Med*. 2010;36(9):1597-601.
3. Zarb P, Coignard B, Griskeviciene J, et al. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveill*. 2012;17(46):20316.
4. Olachea PM, Palomar M, Alvarez-Lerma F, et al. Morbidity and mortality associated with primary and catheter-related bloodstream infections in critically ill patients. *Rev Esp Quimioter*. 2013;26(1):21-9.
5. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol*. 2008;29(11):996-1011.
6. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. *Ann Intensive Care*. 2011;1:47.
7. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118(1):146-55.
8. Muscedere JG, Shorr AF, Jiang X, et al. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: an important determinant of outcome. *J Crit Care*. 2012;27(3):322.e7-14.
9. Manian FA. IDSA Guidelines for the diagnosis and management of intravascular catheter-related bloodstream infection. *Clin Infect Dis*. 2009;49(11):1770-1.
10. Cercenado E, Ena J, Rodriguez-Creixems M, Romero I, Bouza E. A conservative procedure for the diagnosis of catheter-related infections. *Arch Intern Med*. 1990;150(7):1417-20.
11. Fortun J, Perez-Molina JA, Asensio A, et al. Semiquantitative culture of subcutaneous segment for conservative diagnosis of intravascular catheter-related infection. *JPEN J Parenter Enteral Nutr*. 2000;24(4):210-4.
12. Blot F. Diagnosis of catheter-related infections. In: Seifert H, Jansen B, Farr B (Eds). *Catheter-Related Infections*. New York: Marcel Dekker; 2005. Pp. 37-76.
13. Leon M, Garcia M, Herranz MA, et al. Diagnostic value of Gram staining of pericatheter skin and the connection in the prediction of intravascular-catheter-related bacteremia. *Enferm Infecc Microbiol Clin*. 1998;16(5):214-8.
14. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med*. 2004;140(1):18-25.
15. Sabatier C, Garcia X, Ferrer R, et al. Blood culture differential time to positivity enables safe catheter retention in suspected catheter-related bloodstream infection: a randomized controlled trial. *Med Intensiva*. 2015;39(3):135-41.
16. Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. *Lancet*. 1999;354(9184):1071-7.
17. Abdelkefi A, Achour W, Ben Othman T, et al. Difference in time to positivity is useful for the diagnosis of catheter-related bloodstream infection in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2005;35(4):397-401.
18. Bouza E, Alvarado N, Alcalá L, et al. A randomized and prospective study of 3 procedures for the diagnosis of catheter related bloodstream infection without catheter withdrawal. *Clin Infect Dis*. 2007;44(6):820-6.
19. Washington JA 2nd. Blood cultures: principles and techniques. *Mayo Clin Proc*. 1975;50(2):91-8.
20. Washington C, Koneman EW, Allen SD, et al. The Enterobacteriaceae. In: Koneman's Color Atlas and Textbook of Diagnostic Microbiology, 6th edition. Philadelphia: Lippincott Williams and Wilkins; 2006. Pp. 211-302.
21. Fenollar F, Raoult D. Molecular diagnosis of bloodstream infections caused by non cultivable bacteria. *Int J Antimicrob Agents*. 2007;30(Suppl 1):S7-15.
22. Liesenfeld O, Lehman L, Hunfeld KP, et al. Molecular diagnosis of sepsis: New aspects and recent developments. *Eur J Microbiol Immunol (Bp)*. 2014;4(1):1-25.

23. Murray PR, Masur H. Current approaches to the diagnosis of bacterial and fungal bloodstream infections in the intensive care unit. *Crit Care Med*. 2012;40(12):3277-82.
24. Afshari A, Schrenzel J, Ieven M, et al. Bench-to-bedside review: rapid molecular diagnostics for bloodstream infection—a new frontier? *Crit Care*. 2012;16(3):222.
25. Chang SS, Hsieh WH, Liu TS, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis—a systemic review and meta-analysis. *PLoS One*. 2013;8(5):e62323.
26. Lehmann LE, Herpichboehm B, Kost GJ, et al. Cost and mortality prediction using polymerase chain reaction pathogen detection in sepsis: evidence from three observational trials. *Crit Care*. 2010;14(5):R186.
27. Ho YP, Reddy PM. Advances in mass spectrometry for the identification of pathogens. *Mass Spectrom Rev*. 2011;30(6):1203-24.
28. Cherkaoui A, Hibbs J, Emonet S, et al. Comparison of two matrix-assisted laser desorption ionization-time of flight mass spectrometry methods with conventional phenotypic identification for routine identification of bacteria to the species level. *J Clin Microbiol*. 2010;48(4):1169-75.
29. Segawa S, Sawai S, Murata S, et al. Direct application of MALDI-TOF mass spectrometry to cerebrospinal fluid for rapid pathogen identification in a patient with bacterial meningitis. *Clin Chim Acta*. 2014;435:59-61.
30. Alby K, Gilligan PH, Miller MB. Comparison of matrix-assisted laser desorption ionization-time of flight (maldi-tof) mass spectrometry platforms for the identification of Gram-negative rods from patients with cystic fibrosis. *J Clin Microbiol*. 2013;51(11):3852-4.
31. Guembe M, Rodriguez-Sanchez B, Ruiz A, et al. Can MALDI-TOF mass spectrometry be used with intravascular catheters? *Enferm Infec Microbiol Clin*. 2014;32(6):372-4.
32. Wang LJ, Lu XX, Wu W, et al. Application of matrix-assisted laser desorption ionization time-of-flight mass spectrometry in the screening of vanA-positive *Enterococcus faecium*. *Eur J Mass Spectrom*. 2014;20(6):461-5.
33. Hoyos-Mallecot Y, Cabrera-Alvargonzalez JJ, Miranda-Casas C, et al. MALDI-TOFMS, a useful instrument for differentiating metallo- β -lactamases in *Enterobacteriaceae* and *Pseudomonas* spp. *Lett Appl Microbiol*. 2014;58(4):325-9.
34. Johansson A, Nagy E, Söki J, ESGAI(ESCMID Study Group on Anaerobic Infections). Detection of carbapenemase activities of *Bacteroides fragilis* strains with matrix-assisted laser desorption ionization—time of flight mass spectrometry (MALDI-TOFMS). *Anaerobe*. 2014;26:49-52.
35. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.
36. Baselski VS, El-Torky M, Coalson JJ, et al. The standardization of criteria for processing and interpreting laboratory specimens in patients with suspected ventilator-associated pneumonia. *Chest*. 1992;102(5 Suppl 1):571S-9S.
37. Georges H, Santre C, Leroy O, et al. Reliability of quantitative cultures of protected specimen brush after freezing. *Am J Respir Crit Care Med*. 1996;153(2):855-7.
38. de Lassence A, Joly-Guillou ML, Salah A, et al. Accuracy of delayed (24 hours) processing of bronchoalveolar lavage for diagnosing bacterial pneumonia. *Crit Care Med*. 2004;32(3):680-5.
39. Maillet JM, Fitoussi F, Penaud D, et al. Concordance of antibiotic prophylaxis, direct Gram staining and protected brush specimen culture results for postoperative patients with suspected pneumonia. *Eur J Anaesthesiol*. 2006;23(7):563-7.
40. Blot F, Raynard B, Chachaty E, et al. Value of gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*. 2000;162(5):1731-7.
41. Croce MA, Fabian TC, Waddle-Smith L, et al. Utility of Gram's stain and efficacy of quantitative cultures for post-traumatic pneumonia: a prospective study. *Ann Surg*. 1998;227(5):743-51.
42. Prekates A, Nanas S, Argyropoulou A, et al. The diagnostic value of gram stain of bronchoalveolar lavage samples in patients with suspected ventilator associated pneumonia. *Scand J Infect Dis*. 1998;30(1):43-7.
43. Coffin SE, Klompas M, Classen D, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008;29(Suppl 1):S31-40.
44. Masterton RG, Galloway A, French G, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2008;62(1):5-34.
45. Linssen CF, Jacobs JA, Schouten JS, et al. Influence of antibiotic therapy on the cytological diagnosis of ventilator-associated pneumonia. *Intensive Care Med*. 2008;34(5):865-72.
46. Wunderink RG. Surrogate markers and microbiologic end points. *Clin Infect Dis*. 2010;51(Suppl 1):S126-30.
47. Jung B, Embriaco N, Roux F, et al. Microbiological data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score. *Intensive Care Med*. 2010;36(5):790-8.
48. Luyt CE, Guérin V, Combes A, et al. Procalcitonin kinetics as a prognostic marker of ventilator associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(1):48-53.
49. Tenover FC. Developing molecular amplification methods for rapid diagnosis of respiratory tract infections caused by bacterial pathogens. *Clin Infect Dis*. 2011;52(Suppl 4):S338-45.
50. Williams GJ, Macaskill P, Chan SF, et al. Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a meta-analysis. *Lancet Infect Dis*. 2010;10(4):240-50.
51. Robins DG, Rogers KB, White RH, et al. Urine microscopy as an aid to detection of bacteriuria. *Lancet*. 1975;1(7905):476-8.
52. Crout FV, Tilton RC. Rapid screening of urine for significant bacteriuria by Gram stain, acridine orange stain, and the Autobac MTS system. *Diagn Microbiol Infect Dis*. 1984;2(3):179-86.
53. Wiwanitit V, Udomsantisuk N, Boonchalermvichian C. Diagnostic value and cost utility analysis for urine Gram stain and urine microscopic examination as screening tests for urinary tract infection. *Urol Res*. 2005;33(3):220-2.
54. Kallenius G, Dornbusch K, Hallander HO, et al. Comparison of direct and standardized antibiotic susceptibility testing in bacteriuria. *Chemotherapy*. 1981;27(2):99-105.
55. Johnson JR, Tiu FS, Stamm WE. Direct antimicrobial susceptibility testing for acute urinary tract infections in women. *J Clin Microbiol*. 1995;33(9):2316-23.
56. Bronnestam R. Direct antimicrobial susceptibility testing in bacteriuria. *APMIS*. 1999;107(4):437-44.
57. Breteler KB, Rentenaar RJ, Verkaart G, et al. Performance and clinical significance of direct antimicrobial susceptibility testing on urine from hospitalized patients. *Scand J Infect Dis*. 2011;43(10):771-6.
58. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). *Clin Infect Dis*. 2013;57(4):e22-e121.
59. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41(10):1373-406.
60. Sinclair A, Xie X, Teltscher M, et al. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by *Streptococcus pneumoniae*. *J Clin Microbiol*. 2013;51(7):2303-10.
61. de Ory F, Minguito T. Comparison of five commercial assays for the detection of *Legionella pneumophila* antigens in urine. *Enferm Infec Microbiol Clin*. 2009;27(2):81-4.
62. Emmadi R, Boonyaratankornkit JB, Selvarangan R, et al. Molecular methods and platforms for infectious diseases testing: a review of FDA-approved and cleared assays. *J Mol Diagn*. 2011;13(6):583-604.
63. Tenover FC. Potential impact of rapid diagnostic tests on improving antimicrobial use. *Ann NY Acad Sci*. 2010;1213:70-80.
64. Kaldor J, Asznovicz R, Buist DG. Latex agglutination in diagnosis of bacterial infections with special reference to patients with meningitis and septicemia. *Am J Clin Pathol*. 1977;68(2):284-9.

65. Henríquez-Camacho C, Losa J. Biomarkers of sepsis. *Biomed Res Int*. 2014; 2014:547818.
66. Pova P, Coelho L, Almeida E, et al. C-reactive protein as a marker of infection in critically ill patients. *Clin Microbiol Infect* 2005;11(2):101-8.
67. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care*. 2010;14(1):R15.
68. Pova P, Coelho L, Almeida E, et al. Early identification of intensive care unit-acquired infections with daily monitoring of C-reactive protein: a prospective observational study. *Crit Care*. 2006;10(2):R63.
69. Hofer N, Zacharias E, Muller W, et al. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. *Neonatology*. 2012;102(1):25-36.
70. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol*. 2010;48(7):2325-9.
71. Tang BM, Eslick GD, Craig JC, et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7(3):210-7.
72. Wacker C, Prkno A, Brunkhorst F, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-35.
73. Faix JD. Biomarkers of sepsis. *Crit Rev Clin Lab Sci*. 2013;50(1):23-36.
74. Altun C, Almuhayawi M, Ullberg M, et al. Clinical Evaluation of the Film Array Blood Culture Identification Panel in Identification of Bacteria and Yeasts from Positive Blood Culture Bottles. *J Clin Microbiol*. 2013;51(12):4130-6.
75. Buss SN, Leber A, Chapin K, et al. Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. *J Clin Microbiol*. 2015;53(3):915-25.
76. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of the BioFire FilmArray Meningitis/Encephalitis Panel for the Detection of Bacteria, Viruses and Yeast in Cerebrospinal Fluid Specimens. *J Clin Microbiol*. 2016; 54(9):2251-61.
77. Magadia RR, Weinstein MP. Laboratory diagnosis of bacteremia and fungemia. *Infect Dis Clin North Am*. 2001;15(4):1009-24.
78. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. *Ann Intensive Care*. 2011;1:37.
79. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Disease Society of America. *Clin Infect Dis*. 2008;46(3):327-60.
80. Denning DW. Aspergillosis. In: Longo DL, Fauci SA, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (Eds). *Harrison's Principles of Internal Medicine*, 18th edition. USA: McGraw-Hill Companies, Inc; 2012. Pp. 1655-60.
81. Dominic RS, Prashanth H, Shenoy S, et al. Diagnostic value of latex agglutination in cryptococcal meningitis. *J Lab Physicians*. 2009;1(2):67-8.
82. Thomson CR. Development of an immunochromatographic lateral-flow device for rapid serodiagnosis of Invasive Aspergillosis. *Clin Vaccine Immunol*. 2008;15(1):1095-105.
83. Pfaller MA, Wolk DM, Lowery TJ. T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. *Future Microbiol*. 2016;11(1):103-17.
84. Prod'homme G, Bizzini A, Durussel C, et al. Matrix-assisted laser desorption ionization-time of flight mass spectrometry for direct bacterial identification from positive blood culture pellets. *J Clin Microbiol*. 2010;48(4):1481-3.

Biomarkers in Invasive Fungal Infections

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INTRODUCTION

There has been a considerable increase in the incidence of invasive fungal infections (IFIs) in intensive care unit (ICU). Till recently, only when the bacterial cultures were negative and the patient had not improved on empiric antibacterial therapy would it dawn upon the clinician that they may be dealing with a fungal infection. The scenario is, however, changing now as the settings in which fungal pathogens are involved are better identified and the means to treat them are becoming available. The principal fungal pathogens involved in the ICU are *Candida* and *Aspergillus*. *Cryptococcus* and other yeasts as well as *Mucor* and other molds are less common. Since the fungal infections are associated with high mortality, a high index of suspicion is required for early diagnosis and treatment initiation, which is crucial for a successful outcome. Unfortunately, blood or other body fluid cultures are not often positive, and invasive procedures to make a tissue diagnosis are not possible due to many factors like thrombocytopenia, neutropenia, etc. in patients at risk for infection with these pathogens. To overcome this problem, nonculture-based methods like fungal biomarkers can be useful clinical tools. These tests may at times become positive even before signs and symptoms of clinical disease appear and can help to initiate pre-emptive antifungal therapy. Here, the authors present an overview of biomarkers in IFI and their utility in ICU.¹

INVASIVE CANDIDIASIS IN INTENSIVE CARE UNIT

Candida is the most common opportunistic fungus causing invasive infection in the ICU. Colonization is the first step in the development of invasive candidiasis followed by invasion due to breach in skin or gut integrity. Neutropenia and prolonged use of antibiotics favor invasion and dissemination of *Candida*. Other risk factors are critical illness with prolonged ICU stay and indwelling vascular devices, total parenteral nutrition, hemodialysis, pancreatitis, gastrointestinal (GI) perforation, surgery, and steroids.¹

The incidence of ICU-acquired candidemia in India is 6.51 cases/1,000 ICU admissions which are 20–30 times higher compared to western world.^{2,3}

The most commonly isolated *Candida* species in India is *Candida tropicalis* followed by *Candida albicans*, and *Candida parapsilosis*. The median duration of onset of candidemia in ICU is 8 days, which is earlier as compared to the West.⁴

Blood culture is the gold standard for the diagnosis of candidemia, but it takes more than 48 hours to become positive and rate of culture positivity in India is 21%, which is lower than the West.² It has been shown that a delay of each day in initiating antifungal therapy after the onset of candidemia increases the risk of mortality. The risk of mortality is 15%, if antifungal treatment was started on the same day when blood cultures became positive which increases to 24%, 37%, and 40% with initiation of treatment on days 1, 2, and ≥ 3 , respectively. For this reason, nonculture-based methods can be the key to early diagnosis. The use of serum biomarkers in the diagnosis of invasive *Candida* infections can therefore be useful.

Biomarkers of *Candida*^{1,5} (Table 1)

Beta-D-glucan

It is a cell wall component of major fungi including *Candida* species, *Aspergillus* species, and *Pneumocystis jiroveci*. The Beta-D-glucan assay (Fungitell) has been approved by the US Food and Drug Administration (FDA). Sensitivity and specificity for diagnosing invasive candidiasis is 75–80% and 80%, respectively.

Mannan Antigen and Anti-mannan Antibodies

Mannan is a component of *Candida* cell wall (7% of total dry cell weight), released in blood circulation during candidemia. It is short-lived due to rapid clearance followed by appearance of anti-mannan antibody.

TABLE 1 Biomarkers in *Candidiasis*

Biomarker	Usefulness	Limitations
β -D-glucan	<ul style="list-style-type: none"> • Pan fungal marker • Positive result may occur days-to-weeks prior to positive blood culture • Serial values are useful for assessing response to treatment 	<ul style="list-style-type: none"> • Technically difficult • False-positive result (Gram-positive and Gram-negative bacteremia, IV amoxicillin-clavulanate, hemodialysis, fungal colonization, IV albumin or IVIG, use of surgical gauze or other material containing glucan and mucositis) • Uncertainties still remain about the best cutoff value for a positive result, number of positive tests required to make a diagnosis, and optimal timing and frequency of testing among at-risk patients • Usefulness in children • Testing on sample other than serum
Mannan antigen Antimannan antibody	<ul style="list-style-type: none"> • Good performance for <i>albicans</i>, <i>tropicalis</i>, <i>glabrata</i> where blood culture is typically negative • Sensitivity highest for <i>Candida albicans</i> • Positive test has been recorded several days before radiological detection of hepatosplenic <i>Candidiasis</i> • When the test is combined with simultaneous mannan detection, the sensitivity and specificity values improve to 83% and 86%, respectively 	<ul style="list-style-type: none"> • Rapidly cleared from blood and frequent testing is required in high risk patients • Antibody detection is unreliable in immunocompromised patient
PCR	<ul style="list-style-type: none"> • High sensitivity (95%) and specificity (92%) 	<ul style="list-style-type: none"> • Lack of standardized methodologies • Technically difficult • Does not give information about species and susceptibility • Less useful unless done 24 x 7 • Role of PCR in testing samples other than blood is not known

IV intravenous; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction.

Polymerase Chain Reaction

Molecular diagnosis by polymerase chain reaction (PCR) allows the detection of fungal deoxyribonucleic acid (DNA) in the blood of patients before conventional methods can detect the fungi.

INVASIVE ASPERGILLOSIS IN INTENSIVE CARE UNIT

The true incidence of invasive pulmonary aspergillosis (IPA) in ICU is difficult to quantify. Diagnostic issues include difficulty in differentiating colonization and invasion, diagnostic criteria [European Organization for Research and Treatment of Cancer/IFIs Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG criteria) are useful for clinical studies on the hematologic malignancy population] are not validated for the ICU population. Besides biomarkers [galactomannan (GM)] are not yet validated for the ICU population. Finally, very few institutions perform autopsies which give the true picture. However, risk categorization has been attempted with some success⁶ (Box 1).

Box 1: Risk categories of patients for invasive aspergillosis

- High risk
 - Neutropenia (neutrophil count $<500/\text{mm}^3$)
 - Hematologic malignancy
 - Allogeneic bone marrow transplantation
- Intermediate risk
 - Prolonged treatment with corticosteroids before admission to ICU
 - Autologous bone marrow transplantation
 - Chronic obstructive pulmonary disease
 - Liver cirrhosis with duration of stay >7 days in ICU
 - Solid organ tumor
 - HIV infection
 - Lung transplantation
 - Systemic diseases requiring immunosuppressive therapy
- Low risk
 - Severe burns
 - Other SOT (heart, kidney and liver recipients)
 - Steroid treatment for less than 7 days
 - Prolonged stay in ICU >21 days
 - Malnutrition
 - Postcardiac surgery status

ICU, intensive care unit; HIV, human immunodeficiency virus; SOT, solid-organ transplant

Biomarkers in Aspergillosis

Galactomannan (Tables 2–4)

Galactomannan is a heat stable heteropolysaccharide consisting of a nonimmunogenic mannan core with immune reactive galactofuranosyl units, which is released during hyphal growth.⁷ Being an antigen and an early indicator of disease, it can be detected in blood even before clinical or radiologic features of disease appear.

The value of GM [serum and bronchoalveolar lavage (BAL)] in aiding the diagnosis of IPA has been studied extensively, especially in the neutropenic, and hematologic malignancy populations, and has been included in the EORTC/MSG criteria.

But there are some false-positive and false-negative results of GM.⁸ Despite these shortcomings it has excellent diagnostic value when used appropriately.

TABLE 2 False positives and false negatives with galactomannan⁸

False-positive results	False-negative results
Other fungi can cause a positive result including <i>Penicillium</i> , <i>Histoplasma capsulatum</i> , <i>Fusarium</i>	<i>Aspergillus tracheobronchitis</i>
Plasmalyte fluid used in BAL	Non-neutropenic with low-fungal burden (for serum GM)
Beta lactam drugs including piperacillin-tazobactam, amoxy-clavulanic acid, cefepime, ceftriaxone, carbapenems and ampicillin	Anti-aspergillus antibodies present
GI tract mucositis due to translocation of food borne GM, or bacteria with cross-reactive epitopes including <i>Bifidobacterium</i> especially in neonates	Prior mold-active antifungal prophylaxis

BAL, bronchoalveolar lavage; GM, galactomannan; GI, gastrointestinal.

TABLE 3 Sensitivity and specificity of galactomannan in neutropenic population with proven invasive pulmonary aspergillosis

	Sensitivity (%)	Specificity (%)
Serum GM OD 0.5	70	92
BAL GM OD 1	100	80.4

GM, galactomannan; BAL, bronchoalveolar lavage.

TABLE 4 Sensitivity and specificity of galactomannan in non-neutropenic population^{10,11}

	Sensitivity (%)	Specificity (%)
Serum GM	36.8	76.1
BAL GM	94.7	86.2

GM, galactomannan; BAL, bronchoalveolar lavage.

Hematologic Malignancies and Those Undergoing Hematopoietic Stem Cell Transplantation

In this population, due to the higher fungal burden and lower neutrophil counts, the serum GM as well as the BAL GM have good sensitivity and specificity. Bronchoalveolar lavage has a greater sensitivity and a lower specificity.⁹

Non-neutropenic Population

Not much data is available in this population to assess sensitivity and specificity accurately. Although, the BAL GM sensitivity and specificity is not really affected much by presence of neutropenia, it has been shown that neutrophils capture GM from blood by their mannose-binding receptors, thus assay sensitivity is lowered in patients who are non-neutropenic.^{10,11}

Strategies of Testing (Table 5)

There can be two strategies of GM testing in serum. Timely testing can be performed in case of clinical suspicion of IPA (clinic-radiologic finding consistent with IPA) to make a diagnosis of IPA and prompt-directed therapy for probable IPA.

Alternatively, GM can be monitored regularly, in a select group of high risk patients (e.g., 2–3 times/week among oncohematologic patients during the neutropenic phase) in the absence of clinical signs or symptoms for early detection of IPA. In the latter strategy, a positive GM would be the first hint of the disease and trigger further diagnostic workup including computed tomography (CT) scan and bronchoscopy and may prompt pre-emptive therapy.

The cutoff for BAL GM is still debated, but an optical density (OD) of less than 0.5 virtually rules out the diagnosis of IPA, while a value of more than 3 has near 100% specificity.¹¹

Monitoring of Therapeutic Response

Galactomannan is also useful in the follow-up for assessment of therapeutic response. While radiologic signs of improvement are usually delayed, a decline or increase in GM value in serum may be the first indicator toward therapeutic failure or success.

TABLE 5 Rational interpretation of galactomannan assay—the following table demonstrates rational interpretation of the assay¹¹

Value	Sensitivity	Specificity	Significance
>0.5	High	Low	Rules out IPA, if negative
>3	Low	100%	Rules in regardless of pretest probability
0.8	86.4%	90.7%	PPV 81%, NPV 93.6%
0.5–3	–	–	Pretest probability is crucial for interpretation

IPA, invasive pulmonary aspergillosis; NPV, negative predictive values; PPV, positive predictive values.

Polymerase Chain Reaction

A meta-analysis of PCR methods applied to blood, serum and plasma to detect IPA was published in 2009.¹² Analysis using a single positive PCR gave a sensitivity of 88% and specificity of 75%, whereas the requirement of two positive samples made the sensitivity 75% and specificity 87%. Majority of studies involved patients with hematologic malignancy, however, some studies also looked at solid-organ transplant (SOT) recipients. Another meta-analysis of the use of BAL for PCR diagnosis of IPA yielded a sensitivity of 91% and specificity of 92%.¹³

Limitations

Multiple in-house assays exist with differences in DNA extraction, PCR technique and product detection with little or no standardization that can allow comparison of studies. Besides, the extent to which the detection can assist clinical management is not known. Hence, it has not yet been incorporated into the EORTC/MSG criteria.

Polymerase Chain Reaction and Galactomannan

In preliminary studies, it has been shown that PCR positivity precedes GM assay by 2–3 weeks.¹⁴ A prospective trial comparing the use of GM and PCR as compared to GM alone found better performance of the combination as compared to either test alone.¹⁴

Breath Tests

It has been found that in patients with suspected IPA, aspergillus secondary metabolite signatures in breath (α -trans-bergamotene, β -trans-bergamotene, β -vatenene-like sesquiterpene) identified IPA patients with a sensitivity 94% and specificity of 93%. These results provided proof-of-concept that direct detection of fungal metabolites in breath can be used as a novel, noninvasive, pathogen-specific approach to identify patients with IPA.¹⁵

Lateral Flow Device

A novel and simple lateral flow device (LFD) using monoclonal antibody JF5 that targets an extracellular glycoprotein of *Aspergillus* has been developed. The performance of this LFD was compared to real-time PCR (targeting 28S rRNA gene) and GM detection when testing serum from an EORTC/MSG defined hematological population. In proven/probable IPA versus no IPA population, the LFD performance was comparable to both PCR and GM EIA. Specificity (98.0%) was similar to PCR (96.6%) and slightly superior to GM (91.5%). Sensitivity (81.8%) was inferior to PCR (95.5%), but better than GM (77.3%). In combination with PCR, it provided both 100% sensitivity and specificity.^{16,17}

CONCLUSION

Invasive fungal infections are an important challenge in the critically ill patient. Since early diagnosis of definite infection is difficult and treatment delay is to be avoided, new means of making early diagnosis is essential. On the other hand, starting treatment when the sepsis syndrome has already developed leads to delayed therapy and poor outcome. Since the sepsis syndrome could be due to other causes, empirical antifungal therapy may lead to overuse of antifungal agents. Hence, the use of biomarker-assisted diagnosis can achieve the twin goals of maximizing outcomes for the individual patient and minimizing the collateral damage to the microbial ecology of the ICU.

REFERENCES

1. Soman R, Preeti Pillai P. Invasive Fungal Infections: When to Suspect and How to Manage? *Medicine Update*. 2012;22:15-9.
2. Chakrabarti A, Sood P, Rudramurthy SM, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. *Intensive Care Med*. 2015; 41:285-95.
3. Chakrabarti A. Microbiology of systemic fungal infections. *J Postgrad Med*. 2005;51:S16-20.
4. Singh T, Kashyap AK, Ahlwalia G, et al. Epidemiology of fungal infections in critical care setting of a tertiary care teaching hospital in North India: a prospective surveillance study. *J Clin Sci Res*. 2014;3:14-25.
5. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1-50.
6. Meersseman W, Lagrou K, Maertens J, et al. Invasive aspergillosis in the ICU. *Clin Infect Dis*. 2007;45:205-16.
7. Latge JP, Kobayashi H, Debeaupuis JP, et al. Chemical and immunological-characterization of the extracellular galactomannan of *Aspergillus fumigatus*. *Infect Immun*. 1994;62:5424-33.
8. Ambasta A, Carson J, Church DL. The use of biomarkers and molecular methods for the earlier diagnosis of invasive aspergillosis in immunocompromised patients. *Med Mycol*. 2015;53:531-57.
9. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. *Clin Infect Dis*. 2009;49:1688-93.
10. Cordonnier C, Botterel F, Ben Amor R, et al. Correlation between galactomannan antigen levels in serum and neutrophil counts in hematological patients with invasive aspergillosis. *Clin Microbiol Infect*. 2009;15:81-6.
11. D'Haese J, Theunissen K, Vermeulen E, et al. Detection of galactomannan in bronchoalveolar lavage fluid samples of patients at risk for invasive pulmonary aspergillosis; analytical and clinical validity. *J Clin Microbiol*. 2012;50:1258-63.
12. Mengoli C, Cruciani M, Barnes RA, et al. Use of PCR for diagnosis of invasive aspergillosis: systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9:89-96.
13. Sun WK, Zhang F, Xu XY, et al. A systematic review of the accuracy of diagnostic test of serum galactomannan antigen detection for invasive aspergillosis. *Zhonghua Jie He He Hu Xi Za Zhi*. 2010;33:758-65.
14. Aguado JM, Vazquez L, Fernandez-Ruiz M, et al. Serum galactomannan versus a combination of galactomannan and polymerase chain reaction-based aspergillus DNA detection for early therapy of invasive aspergillosis in high risk hematological patients: randomized controlled trial. *Clin Infect Dis*. 2015;60:405-14.
15. Koo S, Thomas HR, Daniels SD, et al. Breath fungal secondary metabolite signature to diagnose invasive Aspergillosis. *Clin Infect Dis*. 2014;59:1733-40.
16. White PL, Parr C, Thornton C, et al. An Evaluation of real-time PCR, Galactomannan ELISA and a novel Lateral-Flow Device for the diagnosis of invasive aspergillosis. *J Clin Microbiol*. 2013;51:1510-6.
17. Steinbach WJ. Galactomannan and 1,3- β -D-Glucan Testing for the Diagnosis of Invasive Aspergillosis. *J Fungi*. 2016;2:22.

Extracorporeal Therapies for Sepsis: Current Status

Deven Juneja, Yash Javeri, Anish Gupta, Omender Singh

"Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

—Sir William Osler

INTRODUCTION

Sepsis develops when the initial appropriate host response to infection gets amplified, disproportional, or dysregulated.¹ The mortality from sepsis and septic shock still remains high despite the best of clinical practices. This fosters a continuous search for novel therapies that go beyond objective correction of oxygenation, hemodynamic, and other objective clinical parameters. Research continues investigating the modulation of the inflammatory response for limiting the harmful action of the bacterial products.² Endotoxin, cytokine, and various other mediators of sepsis lead to immune dysfunction, which further cascades and presents as physiological perturbations linked to sepsis.³ Extracorporeal therapies (ECTs) have evidence in endotoxin removal and clinical utility in management of critically ill septic patients.⁴ The physiological basis is strong with favorable clinical outcomes. There are multiple options available to the clinicians to choose from. However, selection criteria and outcomes need to be judiciously understood. Over the last decade, multiple extracorporeal techniques have evolved with the intent of influencing the circulating levels of different inflammatory mediators.⁴

Extracorporeal therapies as adjuvant to conventional medical care may be effective in improving clinical outcomes in a selective subset of critically ill patients diagnosed with sepsis. An adjuvant (from Latin, *adiuvare*: to aid) is a pharmacological or immunological agent that modifies the effect of conventional therapies, which are essentially standard of care. Extracorporeal therapies may be utilized as adjuvant therapies for critically ill septic patients.

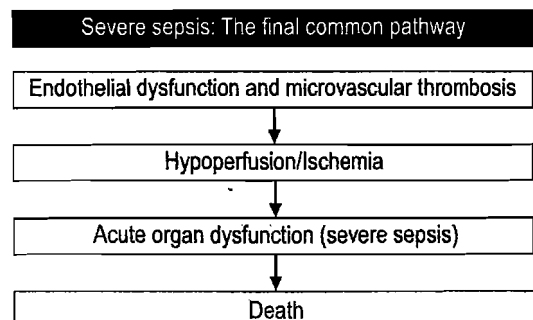
PHYSIOLOGICAL BASIS

Pathobiology of sepsis is explained by organ dysfunction caused by dysregulated host response to infection

(Flowchart 1). Sepsis treatment should follow the trident approach with judicious antimicrobials, immunomodulation, and multiorgan support therapy (MOST). Sepsis is a complex cascade of cellular and humoral network. It is the result of inappropriate and global activation or deactivation of innate immune, inflammatory, thrombotic, and metabolic pathways. There is "immune confusion" and widespread dysregulated inflammation with mediators damaging bystander organs leading to organ dysfunction.³ Recognizing the fact that there is a need for other treatment modalities apart from antibiotics, new additional approaches to stop the sepsis cascade at different levels have been developed.

Endotoxin or lipopolysaccharides (LPS) is one of the major components of the cell membrane in Gram-negative bacteria. When the bacteria are lysed the endotoxin is released. Another major endogenous source of endotoxin is mucosal barrier injury in the gut.⁵

Endotoxin is the principal alarm molecule and the most potent microbial mediator in the pathogenesis of sepsis. Endotoxins are detectable in most septic patients and elevated levels are associated with worse clinical outcomes.⁶ There is a strong evidence linking sepsis to direct and indirect effects of endotoxins. Thus, it may seem prudent to antagonize and/or remove endotoxins in critically ill septic patients. Immunomodulation has a very firm physiological basis with strong clinical plausibility for utilizing ECTs for sepsis.⁷



FLOWCHART 1: Sepsis physiopathogenesis

Over the last 40 years, numerous trials of adjuvant therapies have been conducted in critically ill septic patients. Generally, the results have been less promising in larger trials. Most adjuvant therapies failed to show significant survival benefit. An ideal therapy should precisely modulate sepsis cascade by various mechanisms without any deleterious effect on physiological functions.⁸

Cytokine theory of sepsis suggests pivotal role of various cytokines in sepsis. Augmentation of a local response into a systemic immune response leads to activation of many signaling pathways manifesting as "cytokine storm". Effective reduction of cytokine and other mediator modulates the immune response. An extracorporeal intervention decreases the danger-associated molecular pattern-based excessive proinflammatory response.⁹

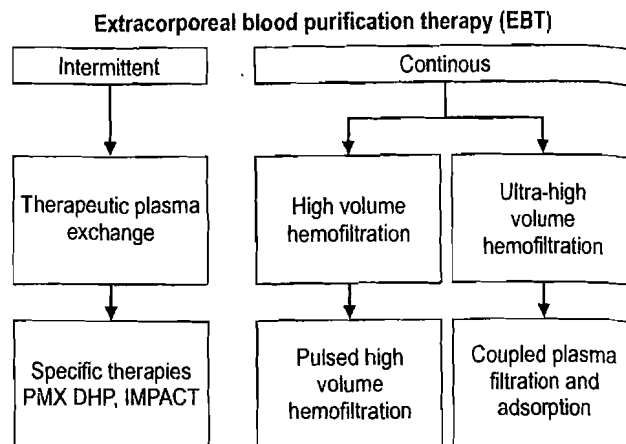
"Peak concentration" hypothesis is based on animal models where injection of endotoxins is followed by serial peaks of mediators. Initially, proinflammatory mediators overwhelm, which is subsequently followed by an increase in anti-inflammatory mediators.^{10,11} The "peak concentration" hypothesis further hypothesizes that a nonselective control of the peaks of inflammation and immunoparalysis may help to restore immune homeostasis. The control of such a nonlinear system cannot be done by simple blockade or elimination of a few specific mediators.¹² Nonselective control of these peaks of systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome may contribute to lesser immune disarray bringing the patient to nearly normal immune homeostasis.¹³

"Threshold modulation" theory explains cytokine system in a very dynamic and comprehensive manner. It suggests that the mediators of sepsis are extricated from body to alter tissue cytokine concentrations and the proinflammatory cascade is halted and controlled when cytokines fall to a particular "threshold" level. "Mediator delivery" theory is the basis for high-volume hemofiltration (HVHF). Higher incoming fluid volumes (3–6 L/h) augments lymph flow by about 20–40 times producing "Drag" of mediators and cytokines with lymph circulation. This lymphatic pull drags cytokines from tissues to blood and hastens extracorporeal removal leading to fall in tissue levels.¹⁴

"The cytokinetic model" theory postulates that removal of sepsis mediators from blood provides a cytokine/chemokine concentration gradient from plasma to site of infection. This drives leukocyte traffic toward the nidus of infection. The bacterial clearance is increased along with cytokine clearance by this mechanism.¹⁵

TECHNOLOGY REVIEW (FLOWCHART 2)

Various renal replacement therapies have been used as adjuvant therapies in the management of patients with sepsis and septic shock. The aim has been to clear "septic solutes". Renal replacement therapies like continuous renal replacement therapy (CRRT), HVHF, and coupled plasma



PMX-DHP, polymyxin direct hemoperfusion.

FLOWCHART 2: Extracorporeal therapies for sepsis

filtration adsorption (CPFA) have been tried extensively with varied results. Elimination and neutralization of endotoxins have been tried using several therapies including ulinastatin, immunoglobulin-M enriched immunoglobulins, adsorber technology, plasmapheresis or CRRT. Presently, inhibition of endotoxin activity with the help of antagonistic synthetic partial endotoxin structures has the strongest body of evidence.

CONTINUOUS RENAL REPLACEMENT THERAPY FOR SEPSIS

The use of CRRT as a treatment option for sepsis has arisen not only because of its benefits in fluid and electrolyte management, but also from its ability to extricate many of the mediators of sepsis to certain extent. Hence, use of CRRT in septic patients may not only be supportive but rather therapeutic. Lack of specificity of removal of mediators and inhibitors of sepsis remain a major drawback. Some studies have shown beneficial clinical effects in spite of no changes in serum cytokine levels. It has been suggested that absolute mediator value measurements may be less helpful than local/tissue levels. However, conventional CRRT (conventional filters and flow rates) has yielded suboptimal results to be recommended as an adjuvant modality for routine management of patients with sepsis.¹⁶

Efficacy of simple diffusive transport with continuous venovenous hemodialysis or convection-based transport at low volumes, as in continuous venovenous hemofiltration in sepsis without acute renal failure has still not got required evidence. Hence, the focus shifted toward other therapies utilizing higher ultrafiltration rates and/or adsorption enabling a higher clearance of middle- and high-molecular weight mediators of sepsis.

HEMOFILTRATION

Hemofiltration can bind and extract large amounts of circulating cytokines and it simultaneously helps in

controlling volume and solute load. Higher doses have been tried with an aim of controlling inflammation. High-volume hemofiltration has been tried in dosage of an average of over 45 mL/kg/h delivered either continuously or in pulsed manner. Clinical benefits shown with small trials were reduction in vasopressor requirement and reduced mortality rates.¹⁷ However, no direct effect of the technique could be shown on the circulating cytokine levels. Hence, the reason behind any benefit is uncertain, although reductions in apoptotic and anaphylactic mediators have been suggested. This therapy has inherent drawbacks including high cost, medication and nutrient losses, and the associated procedural risks.

PLASMAPHERESIS

Plasma filtration has been long tried as a therapy to curtail inflammatory mediators. Plasma exchange separates plasma from whole blood and exchanges the plasma with normal saline, albumin or fresh frozen plasma. Plasma exchange thus could improve sepsis outcomes through removal of harmful substances or by replacement of depleted blood components. However, presently there is limited data but some suggestions of improvements, particularly in Gram negative sepsis have been observed. Technical modification-linking plasma filtration to devices allows adsorption of specific molecules. In coupled plasma filtration, the plasma is returned to the patient, hence avoiding the need for fluid replacement. Initial studies suggested CPFA can lower proinflammatory cytokines with a tendency toward improved hemodynamics and less-organ dysfunction. However, the current evidence is very limited and further studies are required.¹⁸ Presently, there is insufficient evidence about plasma exchange for patients with sepsis or septic shock.

EXTRACORPOREAL ADJUVANT THERAPIES (TABLE 1)

Toraymyxin

Polymyxin B direct hemoperfusion (PMX B DHP) is not only endotoxin adsorption column, but also a hemoperfusion device-modulating sepsis cascade at multiple levels through different mechanisms. These varied mechanisms of action improve organ dysfunction, which may translate into survival benefit.^{20,21} Toraymyxin filter is filled with polystyrene derivative fiber immobilized by PMX B. Polystyrene of the outer side and PMX B are covalently bonded through a chemical process. In addition, the surface of the fiber is porous. Polymyxin B, itself has a great affinity to bind endotoxins.

Procedure

This is the simplest hemopurification in which whole blood is perfused directly by the PMX column. A double-lumen

TABLE 1 Comparison between various extracorporeal therapies

	Low hemolysis	Removes bilirubin	Removes cytokines	Removes endotoxins
I.M.P.A.C.T System* Hemolife	Yes	Yes	Yes	Yes
MARS Baxter/Gambro	No	Yes	No	No
Prometheus Fresenius	Yes	Yes	No	No
CytoSorb™ Cytosorbents	No	No	Yes	No
PMX Toray/Spectral	No	No	No	Yes

MARS, monitoring, analysis and response system; PMX, polymyxin.

dialysis catheter is used for vascular access. The blood is directly perfused (DHP) at flow rate (Qb) of 80–120 mL/min. Standard duration of perfusion is 2 hours. Heparin is generally used as an anticoagulant.

I.M.P.A.C.T. System®

The I.M.P.A.C.T. system® device passes a portion of the plasma through the adsorption column. On an average, during a 4 hour treatment, all of the patient's plasma will have passed twice through the exclusive heart-lung machine (HLM)-100 adsorption column for detoxification.¹⁹ The patient's venous blood first passes through the cellular exclusion column (HLM-200) where plasma and any associated toxins are directed to an adsorption column (HLM-100) and the remaining blood components are returned to the patient. As there is minimal contact with the blood components, the chances of hemolysis are very low. The most important part of the I.M.P.A.C.T system® is the HLM-100 plasma adsorption column, which has a surface area of approximately 200,000 m² and contains a proprietary blend of nonionic adsorbent materials specifically formulated to bind toxins and cytokines associated with liver failure, sepsis, and other disorders.

Biospleen

Biospleen is a novel device for sepsis therapy inspired by the functioning of spleen. Biospleen continuously removes pathogens and toxins from blood without first identifying the infectious agent. Blood flowing from an infected individual is mixed with magnetic nanobeads, which are coated with an engineered human opsonin [mannose-binding lectin (MBL)]. The MBL captures a broad range of pathogens and toxins without activating complement factors or coagulation. The magnetic nanobeads pull the opsonin-bound pathogens and toxins from the blood and the purified blood is then returned to the patient.²⁰

CYTOKINE-BINDING THERAPY

Specific cartridges that absorb cytokines have also been studied extensively in management of sepsis. CytoSorb[®], which utilizes a synthetic polymer-based cytokine-absorbent system, is a representative of this class. This technology is based on very porous, biocompatible polymer beads, which may be helpful in eliminating several sepsis mediators like tumor necrosis factor- α , interleukin (IL)-6, and IL-1. CytoSorb[®] cartridges have been shown to be effective in clearing cytokines with moderate clinical benefits.

High Cut-off Membrane

Higher molecular weight cut-off membranes have larger pore diameters of up to 10 nm. These may be useful in removing cytokines, due to their size. A few pilot studies showed better extraction of a few cytokines with better hemodynamic stability after therapy.²² However, given concerns about cost and higher loss of nutrients, medications, albumin, and other proteins, and more data of clinical benefits will be needed before moving toward its clinical application.

Prismaflex eXeed™ System

Prismaflex eXeed™ system has two filters and may be used for management of sepsis patients with acute kidney injury (AKI). SepteX™ and oXiris™ are proprietary disposable sets used only in conjunction with the Prismaflex™ system. Most of the sepsis mediators are large-molecular weight (approximately 5–50 kDa) substances and are poorly removed by standard high-flux membranes of CRRT. SepteX™ removes larger molecular weight substances through diffusion. SepteX™ has specially designed membrane with pore sizes that allow for the removal of molecules in the inflammatory mediator range. The base membrane material is very similar to that used in Prismaflex™ hemofiltration filter.

On the other hand, the membrane comprising the filter in the oXiris™ set is AN69, which removes endotoxin by adsorption and provides renal support by usual diffusive and convective therapies. The oXiris™ membrane is additionally grafted with heparin making it hemocompatible.²³ Preheparinized membrane is a simpler and safer alternative to circuit heparinization. The oXiris™ membrane is modified suiting patients in AKI and sepsis as it combines cytokine and endotoxin adsorption together with low a thrombogenic CRRT membrane.

Alteco[®] Lipopolysaccharide Adsorber

Alteco[®] LPS adsorber has a synthetic peptide, which is tailored to selectively bind endotoxins. It has high affinity to the lipid A moiety of the endotoxin because of hydrophobic and ionic interactions, which ensures efficient reduction of endotoxins.²⁴

MATISSE[®]-Fresenius System

MATISSE[®]-Fresenius system is based on the endotoxin-binding abilities of human albumin. MATISSE[®] adsorber contains human serum albumin immobilized on polymethacrylate beads.²⁵

CELL-BASED THERAPIES

Extracorporeal techniques have been modified to expose circulating blood to cells outside the body in order to add antimicrobial or inflammatory-modulating properties. One experimental technique separates patient plasma and then passes it through a cartridge of donor granulocytes for extricating sepsis mediators. Animal studies and small human studies have suggested significant benefits.²⁶

PROCEDURAL ASPECTS

Extracorporeal filters are used on dialysis machine. The blood from patient flows through the cartridge, which removes the sepsis mediators. Various anticoagulants like heparin in a dose of 3,000 U bolus followed by an infusion of 20 U/kg/h may be used. Blood flow rate of 100 (80–120) mL/min is required for PMX-DHP. Continuous renal replacement therapy machine or hemodialysis machine may be used for this therapy. Duration and frequency of therapy vary between products. Platelet count, prothrombin time/activated partial thromboplastin time and activated clotting time need to be monitored.

CONTRAINDICATIONS AND CAUTIONS

Known hypersensitivity or allergy to PMX B, or chemicals associated in the therapy. Conditions where the use of heparin would cause a tendency to uncontrolled hemorrhage or in patients in whom adequate anticoagulant therapy cannot be safely achieved, like in cases of hemophilia, etc. is also contraindication. Platelets $<30,000$ cells/mm³ remain a relative contraindication for most extracorporeal systems. Futility of care should also be considered before offering such therapy, as there are associated complications and financial implications. Pharmacoeconomics remains a major-deciding factor for using these therapies.

EVIDENCE

Adjuvant therapies are promising showing clinical plausibility. However, in this era of evidence-based medicine, they pose a difficult challenge of proving significant survival benefit. Mainly single-center or small studies show therapeutic benefit on outcome and these positive results are often contradicted by large multicenter trials. Nevertheless, from a pathophysiological point of view, most of these

therapeutic modalities have a firm rationale. Extracorporeal therapies for sepsis limited with limited evidence.²⁷

A limited body of clinical evidence suggests that neutralization or removal of bacterial LPS endotoxin would be a successful adjunctive approach in the treatment of Gram-negative sepsis. A recent systematic review has indicated some evidence for the efficacy of this approach, although randomized controlled trials are few. An approach using PMX bound to a solid-phase carrier for specific hemo-adsorption in patients with sepsis has been shown to retain the LPS-binding properties of the compound, but minimizes systemic toxic effects. More prospective multicenter data in large-patient populations are needed to confirm or negate the benefits of endotoxin removal in human sepsis. A number of synthetic anti-LPS peptides have shown *in vivo* data indicating beneficial effects on cytokine release and survival.

Polymyxin, PMX B immobilized fiber device has been used safely in the clinical settings in Japan since 1994 for the treatment of severe sepsis and septic shock. Over the last decade, its clinical application is expanding outside of Japan, mainly in Europe and some Asian countries such as India, Taiwan, and Korea. Survival benefit has been reported by the meta-analysis and some controlled studies.²⁸ Also, the improvement of organ dysfunction such as hemodynamic abnormalities has been reported in the clinical studies.

One of the most comprehensive analyses till date of overall clinical experience with this device remains a meta-analysis of 28 studies between 1998 and 2006 conducted by Cruz et al.²⁹ This showed that PMX hemoperfusion was associated with improved blood pressure and a reduction in dopamine dose, better partial arterial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio and reduced mortality. The same group conducted a prospective multicenter randomized controlled trial in patients with severe sepsis or septic shock who required emergency surgery due to intra-abdominal infection in 10 Italian tertiary care intensive care units. A total of 64 patients were enrolled and randomized to the conventional therapy group in accordance with the Surviving Sepsis Campaign guideline ($n = 30$) and the PMX group, which was treated with both the conventional therapy and PMX ($n = 34$).³⁰

As a result, mean arterial pressure increased and vasopressor requirement decreased at 72 hours in the PMX group, but not in the conventional therapy group. The $\text{PaO}_2/\text{FiO}_2$ ratio increased slightly in the PMX group. Sequential organ failure assessment (SOFA) scores improved in the PMX group, but not in the conventional group, and 28-day mortality was 32% in the PMX group and 53% in the conventional group (adjusted hazard ratio, 0.36, 95% confidence interval 0.16–0.80). Evaluating Use of PMX B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES) study results are expected by 2017.

PATIENT SELECTION

Adjunctive therapies are generally used for patients with profound septic shock, as indicated by need for high-vasopressor support and at least two organs dysfunction. Patient selection for initiating adjuvant therapies is still largely based on the physician's "gut feeling" rather than objective parameters and biomarker guidance.

Dynamic procalcitonin (PCT) levels, endotoxin activity assay, and cytokine panels can be used to guide therapy in such patients. However, experience with these markers in regards to initiating adjuvant therapies is limited. Multimodal and individualized approach may help us to tailor these therapies better. The "multimodal" approach means that several clinical and biochemical parameters are taken into account simultaneously, while "individualized" refers to the interpretation of changes/kinetics of certain parameters such as PCT, rather taking only "fixed" absolute values into account. Targeting endotoxin early in the sepsis clinical presentation could help reverse or limit this disease before the cascade reaction becomes overwhelming.³⁰ The various criteria which may be used for patient selection for initiation of adjuvant therapies are given in box 1.

INITIATING THERAPY

Various interventions may be applied at successive points in the cascade, such as antibiotics, therapy directed against endotoxins, extracorporeal techniques to ameliorate the levels of proinflammatory mediators, immunomodulating drugs, and at the far end of the cascade, individual organ support. Organ function is a time-dependent function requiring timely interventions in judiciously selected patients. Therapy offered very late in morbidly ill patients with refractory shock often proves futile.

EXPECTATIONS

It is understood that sepsis care is comprehensive. Immune homeostasis is the primary aim of such therapies. This should further translate into improved microcirculation. Improved

Box 1: Variables for patient Selection for adjuvant therapy

- Severity of sepsis- Utilize objective and subjective criteria
- Sepsis induced organ failure – SOFA score
- Biomarkers – EAA, Cytokine panel, PCT
- Kinetics of biomarkers
- Physiological parameters – perfusion, hemodynamics and oxygenation
- APACHE II
- High risk of death – Any of the following:
 - Refractory shock
 - Sepsis induced ARDS
- No absolute contraindications
- Futility of therapy

microcirculation should gradually show up as stable hemodynamics. Oxygenation indices may also gradually improve. The ultimate measurable effect is a lesser Multiple Organ Dysfunction (MODS) Score. All adjuvant therapies have the ultimate target of survival benefit. The therapies are no magic bullets and will not work as stand-alone therapies. Judicious selection is required after optimal supportive and standardized care.

FUTURE DIRECTIONS

Development of medical evidence remains biggest challenge for the therapy. Pharmacoeconomics also need to be favorable from patient's perspective. Clinicians require a timeline for intervention with this therapy. Clinical criteria should be drafted for easier selection of patients. Clinicians need to look beyond the traditional endpoints of survival benefit with therapies used in critically ill moribund patients. Theranostics methodology should be applied for research and clinical practice where biomarker-guided interventions are done. Collaborative projects with other therapies for sepsis need to be initiated. We need to work on development of an attractive add-on therapy with CRRT/dialysis, extracorporeal membrane oxygenation and cardiopulmonary bypass. Different ECTs have a common physiological basis but are intricately different. We need to have a better understanding about utility of each therapy. We need to find and optimize the best blood purification strategy for treatment of sepsis. A precise understanding of how these therapies work by modulating the cytotoxic and cytokinetic effects of inflammatory mediators is essential.

CONCLUSION

Pathophysiology of sepsis is very complex and still incompletely understood. Several ECTs have shown experimental and clinical utility. Extracorporeal blood purification techniques such as (pulse) high-volume hemofiltration and other high-efficiency techniques have a strong biological treatment rationale, but presently have insufficient clinical evidence. Lipopolysaccharides adsorption have shown efficacy on vasopressor dependency, hemodynamics and survival.

Management of patients with sepsis and septic shock should be comprehensive. Clinicians need to analyze failures and embrace adjuvant modalities in patients at high risk of death. We need to know the options and utilize them at the right time and in the right patient. Multidisciplinary sepsis management remains pivotal. The emergence of ECTs offers new opportunities for sepsis management. Identifying the ideal patient and intervening early is the key to optimal results.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801-10.
2. Vincent JL, Abraham E, Annane D, et al. Reducing mortality in sepsis: New directions. *Crit Care*. 2002;6:S1-18.
3. Rajani-M, Javeri Y, Sangwan KS. Sepsis and antimicrobial therapy in trauma patients. *Int J Curr Adv Res*. 2016;5:915-21.
4. Ronco C, Bonello M, Bordon V, Ricci Z, D'Intini V, Bellomo R, et al. Extracorporeal therapies in non-renal disease: Treatment of sepsis and the peak concentration hypothesis. *Blood Purif*. 2004;22:164-74.
5. Esteban E, Ferrer R, Alsina L, et al. Immunomodulation in sepsis: the role of endotoxin removal by polymyxin B-immobilized cartridge. *Mediators Inflamm*. 2013;2013:507539.
6. Opal SM, Scannon PJ, Vincent JL. Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock. *J Infect Dis*. 1999;180:1584-9.
7. Lenz A, Franklin GA, Cheadle WG. "Systemic inflammation after trauma." *Injury*. 2007;38:1336-45.
8. Hotchkiss RS, Opal S. Immunotherapy for sepsis—a new approach against an ancient foe. *N Engl J Med*. 2010;363:87-9.
9. Ronco C. The immunomodulatory effect of extracorporeal therapies in sepsis: a reconciliation of three theories. *Int J Artif Organs*. 2007;30:855-7.
10. Adrie C, Pinsky MR. The inflammatory balance in human sepsis. *Intensive Care Med*. 2000;26:364-75.
11. Cohen S. "Cytokine: more than a new word, a new concept proposed by Stanley Cohen thirty years ago." *Cytokines*. 2004;28:242-7.
12. Abraham E. Why immunomodulatory therapies have not worked in sepsis. *Intensive Care Med*. 1999;25:556-66.
13. Cole L, Bellomo R, Journois D, et al. High volume hemofiltration in human septic shock. *Intensive Care Med*. 2001;27:978-86.
14. Ratanarat R, Brendolan A, Piccinni P, et al. Pulse high-volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival. *Crit Care*. 2005;9:R294-302.
15. Call DR, Nemzek JA, Ebong SJ. Ratio of local to systemic chemokine concentrations regulates neutrophil recruitment. *Am J Pathol*. 2001;158:715-21.
16. Cole L, Bellomo R, Hart G. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med*. 2002;30:100-6.
17. Joannes-Boyau O, Rapaport S. Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. *ASAIO J*. 2004;50:102-9.
18. Toft P, Schmidt R, Broechner AC. Effect of plasmapheresis on the immune system in endotoxin-induced sepsis. *Blood Purif*. 2008;26:145-50.
19. Hemolife Medical. (2015). I.M.P.A.C.T. System® Extractive Therapy. [online] Available from: http://www.hemolifemedical.com/impact_system_extractive_therapy/. [Accessed November, 2016].
20. Kang JH, Super M, Yung CW, et al. An extracorporeal blood-cleansing device for sepsis therapy. *Nat Med*. 2014;20:1211-6.
21. Zhou F, Peng Z, Murugan R, et al. Blood purification and mortality in sepsis: A meta-analysis of randomized trials. *Crit Care Med*. 2014;41:2209-20.
22. Cruz DN, Perazella MA, Bellomo R, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care*. 2007;11:R47.
23. Turani F. Continuous renal replacement therapy with the adsorbent membrane oXiris in septic patients: a clinical experience. *Critical Care*. 2013;17:P63.
24. Ala-Kokko TI, Laurila J, Koskenkari J. A new endotoxin adsorber in septic shock: Observational case series. *Blood Purif*. 2011;32:303-9.
25. Staubach KH, Boehme M, Zimmermann M, et al. A new endotoxin adsorption device in Gram-negative sepsis: Use of immobilized albumin with the MATISSE adsorber. *Transfus Apher Sci*. 2003;29:93-8.
26. Holmes E, Kinross J, Gibson G. Therapeutic modulation of microbiota-host metabolic interactions. *Sci Transl Med*. 2012;4:137rv6.
27. Pocock SJ. When (not) to stop a clinical trial for benefit. *JAMA*. 2005;294:2228-30.
28. Klein DJ, Foster D, Schorr CA, et al. The EUPHRATES (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial. *Trials*. 2014;15:218.
29. Cruz DN, Perazella MA, Bellomo R. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care*. 2007;11:R47.
30. Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock. The EUPHAS randomized controlled trial. *JAMA*. 2009;301:2445-52.

Optimum Dose of Colistin in Intensive Care Unit

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INTRODUCTION

Infections with multidrug-resistant bacteria, including *Pseudomonas*, *Klebsiella*, *Acinetobacter* and *Escherichia coli* are becoming increasingly common. This becomes even more frequent in hospital-acquired infections especially in patients with immunosuppression and intensive care unit (ICU) patients. Colistin is the mainstay of treating such patients. As there are no new antibiotics in the pipeline to treat carbapenem-resistant Gram-negative organisms, it becomes imperative that we utilize colistin in the optimum way and optimum dosage in order to get the best results and to prevent resistance. Polymyxins, as a group, were discovered in 1947 while colistin was first reported in 1950. It fell into disrepute and the usage was discontinued in 1970s mainly owing to nephrotoxicity. Because of the desperate situation now it has been revived. As it was discovered and approved in 1950s, it did not undergo the stringent preapproval studies, which a drug has to undergo today. Its proper dosage, pharmacokinetics (PK), pharmacodynamics (PD) and toxicity were not clear. Another issue is the presence of heteroresistance in the bacteria, which may lead to development of resistance to colistin during treatment. Various combinations of antibiotics are being tried to overcome this problem. We present a review of literature about the available evidence to optimize the usage of colistin.

COLISTIN PHARMACOLOGY

There are five types of polymyxin (A to E) but only two types are used clinically: polymyxin B and E (colistin). Two different forms of colistin are available commercially:

1. Colistin sulfate
2. Colistin methanesulfonate sodium (CMS).

Colistin methanesulfonate sodium has been found to be less toxic when given parenterally as compared to colistin sulfate. That is why colistin sulfate is used in topical preparation, while CMS is used in intravenous (IV)

preparations. Bergen et al. in 2006 showed that CMS is just a prodrug for colistin and does not have significant intrinsic antimicrobial activity.¹ Another problem is that various pharmaceutical companies label the contents differently some as colistin activity and others as international units (IU) of CMS. The clinician has to be clear about dose in mg or IU of CMS and that of colistin base.²

- One mg of CMS = 0.375 mg of colistin base activity (CBA) = 12,500 IU of colistin
- One mg of colistin base activity = 2.6 mg of CMS = 32,500 IU of colistin.

Following parenteral administration, CMS undergoes hydrolysis *in vivo* to form a complex mixture of colistin and partially sulfomethylated derivatives.³

COLISTIN PHARMACOKINETICS/ PHARMACODYNAMICS

After infusion, CMS hydrolyzes into 13 different products; of which, colistin A and B are major products.⁴ This makes it very difficult to accurately measure the CMS and colistin levels in biological samples.⁵ The PK dispositions of CMS is quite complex. CMS is cleared renally but colistin is cleared nonrenally by undefined mechanisms. In patients with unimpaired renal function as CMS is cleared very fast, it raises a question to the surety of achieving the target levels. In patients who require renal replacement therapy, CMS dosing remains a challenge. In a population PKs study by Garonzik et al., a dose of 112–260 (median 192) mg of CBA per day was required to achieve a target serum concentration of colistin of 1 mg/L.⁶ Colistin has been reported to have 59–74% or as high as 80–90% protein binding (26–41% unbound fraction) in a study of nonburned critically ill patients.⁷ After infusion, the volumes of distribution of polymyxin B, colistin and CMS are 0.4 L/kg, 0.17 L/kg and 0.19 L/kg, which are quite low. All polymyxins tend to accumulate in kidneys, which contribute to renal toxicity.^{8,9} Although only 5% of CMS crosses over into cerebrospinal fluid (CSF) after IV dosing, higher levels

have been achieved by intraventricular administration. In a Greek study by Plachouras et al., 19 patients were studied for postantibiotic effect (PAE). Mean PAEs of 3.90 and 4.48 hour were found for $1 \times$ minimum inhibitory concentration (MIC) and $4 \times$ MIC concentrations of colistin.¹⁰ Absorption from oral mucosa or gastrointestinal tract does not occur. It has shown persistent level in the liver, kidney, heart and muscle while it is poorly distributed to the bones, CSF, lung parenchyma and pleural cavity. Neither CMS nor colistin has shown any significant drug interaction. PK and PD parameters, such as C_{max} /MIC ratio, area under the curve (AUC)/MIC and Time above MIC that could predict the efficacy of colistin, are not clearly defined.¹ Bergen et al. showed that AUC:MIC ratio of total and unbound colistin is the best parameter to predict antibacterial activity.³ Target AUC:MIC values for colistin against *Acinetobacter baumannii* established in mouse thigh and lung models ranged from 17 to 95.⁷ In a population PK study of 105 patients, Grazzoni et al. proposed dosing equations to reach target colistin levels. They postulated that an AUC of 60 mg h/L corresponding to an MIC of 2.5 mg/L may be achieved by their dosing regimens, which may be sufficient to treat an infection due to *A. baumannii* with an MIC less than 1 µg/mL.^{7,11} This dosage may not be sufficient for an infection with an MIC more than 1 mg/mL, but increasing the dosage more than this might create tolerability and toxicity issues. The susceptibility breakpoint for *A. baumannii* to colistin or polymyxin B is 2 µg/mL, as established by the Clinical Laboratory Standards Institute (CLSI). The standard error of the test allows for MIC variance of one doubling dilution. Therefore, a reported MIC of 1 µg/mL may actually be anywhere between 0.5 µg/mL and 2 µg/mL. In a population PK study done by Plachouras et al. 18 patients were given a dose of 3 million IU (MIU) 8 hourly. The predicted maximum plasma concentrations were 0.6 mg/L and 2.3 mg/L. The half-life of colistin was determined to be 14.4 hours. Based on this model, they predicted that given a standard dose of 3 MIU 8 hourly it would take 2–3 days to reach steady state concentrations. They recommended that a loading dose of 9–12 MIU followed by 4.5 MIU 12 hourly would reach the same average steady state concentrations but would reach the target faster.⁸

In a study by Daikos et al., PKs of three different doses of CMS were studied against *Pseudomonas aeruginosa* with an MIC of 1 µg/mL, i.e. 3 MIU 8 hourly, 4.5 MIU 12 hourly and 9 MIU 24 hourly. The C_{max} was found to be 3.34, 2.98 and 5.63 µg/mL, respectively. Complete eradication of *Pseudomonas* was found in samples having a C_{max} of more than 4 µg/mL. While those samples which had an MIC less than 4 µg/mL could demonstrate only 40% killing.⁹

Karnik et al. did a PK study where in they studied 15 patients with proven MDR *Acinetobacter* and *Pseudomonas*. Patients with normal renal function or creatinine clearance of 20–50 mL/min were given a CMS dose of 2 MIU 8 hourly. Those with a creatinine clearance 10–20 mL/min were given a dose of 2 MIU 12 hourly. As per their measurements, the C_{max} /

MIC ratio for *Acinetobacter* was 13.4 after first dose and 26.3 (0.9–64.9) at steady state while that for *Pseudomonas* was 3.18 (1.6–23.1) and 3.82 (2.3–10.9) at steady-state, respectively. This demonstrated that an optimum value of C_{max} /MIC ratio of more than 8 was achieved against *Acinetobacter* but not against *Pseudomonas*.^{12,13}

Pharmacokinetics were studied for 13 patients with ventilator-associated pneumonia. All patients had normal renal function. All were given CMS 2 MIU 8 hourly. The serum levels and BAL levels were measured after 2 days of therapy. They found the serum levels to be suboptimal. Very importantly colistin was totally undetectable in BAL samples.¹⁴

INHALED THERAPY

Despite questionable clinical efficacy of inhaled colistin, the toxicity reported in both prospective and retrospective studies is rather minimal. A 2007 Food and Drug Administration (FDA) MedWatch alert reported one patient death following administration of inhaled colistin that had been premixed by the pharmacy prior to nebulization. The alert concluded that premixing and storing the product in aqueous solution more than 24 hours leads to a greater rate of conversion of CMS to colistin, and may result in toxicity to lung tissue. Thus, in MDR *A. baumannii* pulmonary infections, this therapy may be considered an adjunctive treatment to IV antibiotic therapy. Various studies have evaluated doses of 1.5–4 MU CMS given in 1–3 divided doses.¹⁵

Ratjen et al. evaluated the colistin PKs postinhalation in patients with cystic fibrosis.¹⁶ This study finds that a single dose of CMS (2 MIU) achieved significant higher drug concentration in the sputum even after 12-hour with low level in serum and urine. In a study done by Lu et al. where pneumonia caused by *P. aeruginosa* in piglets and CMS was administered either by nebulization every 12 hours or IV every 8 hours, lung tissue concentration of colistin was measured.¹⁷ Colistin was found undetectable in the lung tissue after IV infusion, while after nebulization, peak lung tissue concentrations were significantly higher in the lung segments (higher in mild pneumonia segments and lower in severe pneumonia area, median 10.0 versus 1.2 µg/g).

As per drug package insert information, the recommended doses of colistin when given by inhalation are as below:¹⁸

- Body weight less than 40 kg: 0.5 MIU (40 mg) of CMS every 12 hours
- Body weight more than 40 kg: 1.0 MIU (80 mg) of CMS every 12 hours
- For recurrent or severe pulmonary infection: 2.0 MIU (160 mg) of CMS every 8 hours.

Optimal inhalation therapy also requires consideration of several factors like position of patient, the type of nebulizer, severity of airway obstruction, aerosol particle size, etc. In a mechanically ventilated patient, there are factors more than this, i.e. artificial airway size, humidity,

gas density, tidal volume, nebulization cycling during inspiration versus continuous, etc. which may affect drug delivery at the target site.⁶

DOSING

Various studies have shown that, if a dose regimen of CMS 3 MIU every 8 hourly is used, it will take 12–48 hours to reach a colistin concentration of 2 mg/L, which is the MIC breakpoint for *A. baumannii* as suggested by EUCAST. The breakpoint, which has been recommended for *Pseudomonas* is even higher at 4 mg/L. It is likely that a low initial concentration would be suboptimal in killing the bacteria, especially in critically ill patients, where an immediate effect is important. Subtherapeutic concentrations may also favor resistance development.¹⁹ This makes the case for giving a loading dose even stronger.

The formation of colistin from CMS and its increase to the steady-state MICs are relatively slow following CMS administration. It is also of importance to consider the protein binding since it is only the unbound fraction (f_u) of the antibiotic that exerts antibacterial activity.¹⁹

In a study conducted in Greece by Mohamed et al., a loading dose of 480 (6 MIU) mg followed by 80–240 mg (1–3 MIU) 8 hourly was given to 10 patients. As per their model increasing the dose from 3 MIU to 6 MIU was predicted to decrease the time to 3 log unit kill from 20 to 8.5 hours. An even shorter time was predicted for a loading dose of 9 MIU. This again highlighted the role of giving a loading dose. A faster kill will likely result in faster resolution of infection. Extending the dosing interval to 12 hours seems to have a limited impact on the bacterial kill. Dosing interval longer than this leads to higher regrowth. In the absence of compelling data demonstrating which definition of body weight to use, it is judicious to use ideal body weight at this time.

Dose Adjustment in Renal Dysfunction

As discussed in PK/PD, CMS is largely cleared through the kidneys. That is why it requires dose adjustment for renal dysfunction. Based on PK data published by Garonzik et al.¹¹ the initial dose of CMS should be similar loading, even for patients with renal impairment. To account for renal dysfunction, the maintenance dose has to be decreased or the dosing interval has to be increased. For renal replacement therapy (RRT)-dependent patients, colistin dose is targeted to reach a serum colistin concentration of 1 mg/L. Among patients dependent upon continuous renal replacement therapy (CRRT), a regimen of 200 mg of CBA (6 MU CMS), divided quaterly 8 hours, is supported by the greatest amount of data (in a total of nine patients). For intermittent hemodialysis (IHD), the doses suggested are much lower, ranging from 30 mg to 70 mg of CBA (0.9–2.0 MU CMS) daily. In patients with residual function, the clearance of CMS is greater particularly on nondialysis days. This leads

to variation in dosing in patients on IHD. This warrants use of a supplemental dose: 30–50% of the daily maintenance dose, following hemodialysis. Dosing equations published by Garonzik et al.¹¹ utilize residual renal function as a factor to determine total daily dose. PK analysis of patients with no residual function predicts a total daily dose requirement of 0.9 MU CMS on nondialysis days and 1.5 MU on dialysis days. Despite scarcity of studies of PK/PD of colistin in patients with renal failure, recent recommended doses are:⁵

- Serum creatinine level 1.3–1.5 mg/dL: 2 MIU (160 mg) of CMS every 8 hours
- Serum creatinine level 1.6–2.5 mg/dL: 2 MIU (160 mg) of CMS every 12 hours
- Serum creatinine level more than or equal to 2.6 mg/dL: 2 MIU (160 mg) of CMS every 24 hours

Patient on Renal Replacement Therapy

- Two MIU (160 mg) of CMS after each hemodialysis
- Two MIU (160 mg) of CMS daily during peritoneal dialysis.

There is no clarity about the exact dose for patients on continuous venovenous hemofiltration or continuous venovenous hemodiafiltration. Karvanen et al. studied the PKs of five critically ill patients on CRRT and concluded that a dose of 160 mg (2 MIU) 8 hourly may be inadequate. Some other studies have suggested that an even higher dose may be required.^{20,21}

CONCLUSION

As colistin is now our last line of defense, the drug has to be used optimally to preserve effectiveness. Based upon PK/PD information, dosing strategies, including loading doses, should be implemented as a means to maximize colistin exposure without delay. The selection of an agent to use in combination with either colistin or polymyxin B has to be individualized as studies have not shown one combination to be superior to other. The clinical decision should include an assessment of the site of infection, susceptibility of the isolate, drug-drug interactions and adverse effects.

REFERENCES

1. Bergen PJ, Li J, Rayner CR, Nation RL. Colistin methanesulfonate is an inactive prodrug of colistin against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2006;50:1953–8.
2. Li J, Nation RL, Turnidge JD. Defining the dosage units for colistin methanesulfonate: urgent need for international harmonization. *Antimicrob Agents Chemother*. 2006;50:4231–2.
3. Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. *Antimicrob Agents Chemother*. 2006;50:2274–5.
4. Orwa JA, Govaerts C, Busson R, et al. Isolation and structural characterization of colistin components. *J Antibiot (Tokyo)*. 2001;54:595–9.
5. Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis*. 2006;6:589–601.

6. Michalopoulos AS, Falagas ME. Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. *Ann Intensive Care*. 2011;1:30.
7. Akers KS, Rowan MP, Niece KL, et al. Colistin pharmacokinetics in burn patients during continuous venovenous hemofiltration. *Antimicrob Agents Chemother*. 2015;59:46-52.
8. Plachouras D, Karvanen M, Friberg LE, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by Gram-negative bacteria. *Antimicrob Agents Chemother*. 2009;53:3430-6.
9. Daikos GL, Skiada A, Pavleas J, et al. Serum bactericidal activity of three different dosing regimens of colistin with implications for optimum clinical use. *J Chemother*. 2010;22:175-8.
10. Plachouras D, Giamarellos-Bourboulis EJ, et al. In vitro postantibiotic effect of colistin on multidrug-resistant *Acinetobacter baumannii*. *Diagn Microbiol Infect Dis*. 2007;57:419-22.
11. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother*. 2011;55:3284-94.
12. Karnik ND, Sridharan K, Jadhav SP, et al. Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection. *Eur J Clin Pharmacol*. 2013;69:1429-36.
13. Bergen PJ, Bulitta JB, Forrest A, et al. Pharmacokinetic/pharmacodynamic investigation of colistin against *Pseudomonas aeruginosa* using an in vitro model. *Antimicrob Agents Chemother*. 2010;54:3783-9.
14. Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate administration. *Chest*. 2010;138:1333-9.
15. Korbila P, Michalopoulos A, Rafailidis PK, et al. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect*. 2010;16:1230-6.
16. Ratjen F, Rietschel E, Kasel D, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother*. 2006;57:306-11.
17. Lu Q, Girardi C, Zhang M, Bouhemad B, et al. Nebulized and intravenous colistin in experimental pneumonia caused by *Pseudomonas aeruginosa*. *Intensive Care Med*. 2010;36:1147-55.
18. Velkov T, Thompson PE, Nation RL, et al. Structure-activity relationships of polymyxin antibiotics. *J Med Chem*. 2010;53:1898-916.
19. Mohamed A F, Karaikos I, Plachouras D, et al. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. *Antimicrob Agents Chemother*. 2012;56:4241-9.
20. Karvanen M, Plachouras D, Friberg LE, et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother*. 2013;57:668-71.
21. Honoré PM, Jacobs R, Joannes-Boyau O, et al. Continuous renal replacement therapy-related strategies to avoid colistin toxicity: a clinically orientated review. *Blood Purif*. 2014;37:291-5.

Early and Empiric Antibiotics in Sepsis: Current Controversy

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INTRODUCTION

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection”.¹ The guidelines for management of sepsis by Surviving Sepsis Campaign (2012) stated that the administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock should be the goal of therapy.² Even the 2015 surviving sepsis care bundle advocates administration of broad-spectrum antibiotic within 3 hours of patient contact. Given the high incidence of emergency department (ED) patients with uncomplicated sepsis who have a substantial chance to progress to severe sepsis,³ and the financial burden associated with severe sepsis, it would be important to explore the rationale behind the early and empirical antibiotic therapy.

RATIONALE FOR EARLY EMPIRIC ANTIBIOTIC THERAPY

The association between time to antibiotics and relevant clinical outcomes has been studied, especially in patients with severe sepsis and septic shock admitted to the intensive care unit (ICU). In four large retrospective studies with overall mortality ranging from 30 to 47%, delayed administration of antibiotics was associated with increased mortality.⁴⁻⁷

1. In a retrospective study conducted by Kumar et al.⁵ in 2,731 septic shock patients, a significant association between delay in effective antibiotic therapy and inhospital mortality after the onset of hypotension ($p < 0.0001$) was noted. A 7.6% decrease in survival for each hour of delay of the antibiotic therapy was noted for the first 6 hours after the onset of shock. In this study, only 50% of the patients received effective antibiotic therapy within the first 6 hours.
2. In a single-center cohort trial by Gaieski et al.⁶ 261 patients with severe sepsis who underwent early goal-directed

therapy (EGDT) time to appropriate antibiotic therapy was significantly associated with reduced mortality.

3. In a retrospective study by Ferrer et al.,⁷ 17,990 patients with severe sepsis and septic shock an hourly increase in mortality with delay in antibiotic administration following recognition of severe sepsis was noted.
4. Garnacho-Montero et al.⁸ reported a prospective observational study of 928 patients admitted to ICU with severe sepsis or septic shock (68% with microbiological identification). They reported that the administration of appropriate and early empirical antimicrobial therapy was associated with a decreased mortality. Progression to septic shock in patients with severe sepsis was also associated with inadequate antimicrobial therapy prior to ICU admission.

CONTROVERSIES

Several studies have suggested that early administration of antibiotics in septic patients reduces mortality, hospital lengths of stay (LOS), and hospital cost.⁹⁻¹² However, these studies were retrospectively conducted and have multiple limitations like variability in the time to antibiotic and quality of initial resuscitation. Patients who are more sick may have received antibiotics early but probably have a higher early mortality, thereby spuriously lowering LOS. The numbers of prospective studies investigating the association between time to antibiotics and outcomes in earlier sepsis stages are very few. Some recent literature suggests that providing early empirical antibiotic therapy may not be effective in the progression of sepsis and may even contribute to more emergence of resistance and complications.

Puskarich et al.¹³ presented results of a multicenter controlled trial in ED (three centers) of 291 patients with septic shock [Emergency Medicine Shock Research Network (EMSHOCK NET)]. The strength of this study is that they prospectively studied the timing of antibiotic administration to ED patients with septic shock. All patients received a

standardized, prescribed early recognition and resuscitation protocol, removing much of the variability in both patient population and early treatment present in other studies. In this study of excellent control for quality of hemodynamic resuscitation and a relatively low mortality of 19%, time to antibiotics was not found to be associated with mortality in septic shock patients, suggesting that hemodynamic resuscitation was more important than early administration of antibiotics. In this study, only administration of antibiotics before the onset of shock was associated with improved outcome. This study had several weaknesses as mentioned below:

- The results may not be generalizable to hospitals without sepsis protocols
- The vast majority of patients received antibiotics within 3 hours and the relatively small numbers of patients in subsequent time points led to wide confidence interval to draw any definitive conclusion
- Although the investigators did not observe significant associations in the study, it is possible that a larger study would be able to detect a difference
- Mortality rate was lower than reports in other septic shock populations
- It was impossible in most cases to identify the exact time of onset of septic shock and thus the timing of antibiotics in relation to onset of shock can often not be ascertained. This is an inherent limitation to the nature of sepsis research
- Given the design of the study, the investigators were only able to draw conclusions regarding associations and not causation.

De Groot et al.⁴ presented a prospective multicenter study conducted in three Dutch EDs which evaluated 1,168 patients with sepsis (stratified into mild, moderate, and severe; overall mortality of 10%) in those receiving antibiotics within 6 hours they reported that a reduction in time to antibiotics was not found to be associated with an improvement in relevant clinical outcomes (28 mortality or LOS).

Sterling et al.¹⁴ conducted a systematic review and meta-analysis of 11 publications (16,178 patients) looking at the association between timing of antibiotic administration and mortality in severe sepsis and septic shock. They also performed sensitivity analysis of the effect of time to antibiotics from severe sepsis or shock recognition in hourly increments. They excluded neutropenic and immunosuppressed patients. The primary outcome was mortality. They did not find statistically significant increase in the pooled odds ratio for mortality for each hourly incremental delay in antibiotic administration.

Apart from the controversy regarding broad-spectrum antibiotic cover, confounding factors impeding early antibiotic therapy should also be considered. Some of these factors may be:

- Presentation level factors:
 - Atypical presentation leading to delayed diagnosis

- Evolution of clinical symptoms and symptoms
- Ability to recognize clinical features
- Requirement for further diagnostic testing
- Patient level factors:
 - Age and comorbid conditions that predispose patients to having atypical presentations
 - History of drug reactions
 - Difficult intravenous access
- System level factors:
 - Emergency department crowding
 - Inadequate staffing
 - Delays in diagnostic testing
 - Patient transfer.

CONCLUSION

It is important to understand that, this controversy challenging the rationale behind early and empirical therapy is not denying the fact that early therapy is not important in severe sepsis and septic shock, but instead it is challenging the arbitrary, nonevidence based time to antibiotic administration of 3 hours (triage) or 1 hour (severe sepsis or shock) as a metric for quality of care. However, despite these current controversies, administering early empirical antibiotics is advocated by all the major guidelines for established or suspected sepsis. Not only this is the current good clinical practice but also medicolegally justified. Unless robust clinical trials and evidences emerge which prove higher risks associated with empirical antibiotic therapy, providing this modality should be practiced by all the healthcare providers.

REFERENCES

1. Singer M, Deutschman CS, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-10.
2. Dellinger RP, Levy MM, Rhodes A, et al. International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
3. Glickman SW, Cairns C, Otero RM, et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. *Acad Emerg Med*. 2010;17(4):383-90.
4. De Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. *Crit Care*. 2015;19:194.
5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-96.
6. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal directed therapy was initiated in the emergency department. *Crit Care Med*. 2010;38(4):1045-53.
7. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-55.

8. Gamacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med*. 2003;31(12):2742-51.
9. Battleman DS, Calahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med*. 2002;162(6):682-8.
10. Rosenstein AH, Hanel JB, Martin C. Timing is everything: Impact of emergency department care on hospital length of stay. *J Clin Outcomes Manage*. 2000;7(8):31-6.
11. Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2004;164(6):637-44.
12. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278(23):2080-4.
13. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med*. 2011;39(9):2066-71.
14. Sterling SA, Miller WR, Pryor J, et al. The Impact of Timing of antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Metaanalysis. *Critical care medicine*. 2015;43(9):1907-15.

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Fever Control in Intensive Care Unit: Is It Helpful?

Prashant Nasa

INTRODUCTION

Fever is a ubiquitous manifestation among patients in intensive care units (ICU), considered commonly as a sign of infection, but can present as an altered host response without infection.^{1,2} Fever has been shown to be associated with increased mortality among patients admitted to ICUs, hence requires attention.^{2,3} Despite fever being known as a cardinal sign of infection for about 120 years, the pathophysiology of its initiation and mechanism of fever is not fully understood.⁴ Management of fever and the association between antipyretic measures and clinical outcomes is also unclear. Definition of fever, its pathophysiology, and current evidence on the utility of treating fever in ICU are discussed in this chapter.

DEFINITION OF FEVER AND ITS MEASUREMENT

The normal body temperature is traditionally taken as 37.0°C (98.6°F) with circadian variation of 0.5–1.0°C.^{5,6} In critically ill patient, the body temperature is affected by many factors like disruption of normal circadian rhythm, need of extracorporeal support or renal replacement therapy, existing acute or chronic organ dysfunctions (like congestive heart failure, chronic liver disease), central or autonomic disturbances, drugs, the ICU ambient environment, and artifacts of measurement.^{6,7} It is, thus, often difficult to determine whether measured abnormal temperature is a reflection of a true pathophysiologic process, or a result of various environmental interactions.⁵ The definition of fever also needs special mention here. The literature has reported different definitions of fever in ICU from single core temperature above 38.0°C to two consecutive elevations above 38.3°C or persistent elevation above 38.3°C for >1 hour.^{6,7} The definition of fever is important because temperature that defines fever if taken lower will increase its

sensitivity but decrease specificity for identifying infection. The Infectious Diseases Society of America and Society of Critical Care Medicine have given a consensus definition of fever as a core body temperature above 38.3°C (>101°F) in nonimmunocompromised ICU patients.⁷ The author have used this definition in this review because of its wider acceptability. It is, however, reasonable to use a lower temperature in immunocompromised patients to define fever.

The technique of consistent and accurate measurement of core body temperature is equally imperative, and temperature measured through thermistor in pulmonary artery catheter is considered as standard for comparison of other devices.^{7,8} The other less invasive methods are thermistor in indwelling bladder catheter, esophageal probe in posterior nasopharynx and lower one-third of esophagus which provide slightly lower temperature, and rectal probes which provide little higher temperature.^{7,8} These devices have been validated for patients in ICU and are considered acceptable alternatives to pulmonary artery catheter, especially for monitoring trends of fever. The less accurate alternative is tympanic membrane using infrared ear thermometry.⁷ The oral and the axillary sites are unreliable and should be avoided in ICU.⁷

PATHOPHYSIOLOGY OF FEVER

The homeostasis mechanism to regulate core body temperature in humans is known as thermoregulation.⁹ This thermoregulation tightly regulates a thermal “set point” with its control area in the preoptic region of the hypothalamus which integrates with other areas in brain, spinal cord, and peripheral receptors in skin, and other core areas in a negative feedback loop. The pathophysiological disturbances of thermoregulation can result in abnormally elevated body temperature.⁹ The abnormal elevated body temperature can be broadly divided into hyperthermia and hyperpyrexia or fever.

TABLE 1 Noninfectious causes of fever in intensive care unit

Inflammatory conditions without infection	Drugs related	Therapy or intervention related	Others
Acute respiratory distress syndrome	Antimicrobials (e.g., β -lactam drugs)	Cytotoxic agents (mainly monoclonal antibodies, granulocyte, and/or monocyte stimulating factor)	Acute coronary syndrome (initial few days)
Aspiration pneumonitis	Antiepileptics (mainly phenytoin)	Jarisch-Herxheimer reaction	Cerebrovascular accident
Acalculous cholecystitis	Antiarrhythmics (mainly quinidine and procainamide)	Postoperative fever up to 48 h	Gastrointestinal bleeding
Gout/pseudogout	Antihistamines	Tumor lysis syndrome	Intestinal/limb ischemia
Head injury	Anti-Parkinson drugs	Transfusion of blood and blood products	Thromboembolism
Malignancy	Antihypertensives, mainly methyldopa, hydralazine	—	Transplant rejection
Pancreatitis	Antimalarials	—	—
Phlebitis/thrombophlebitis	Butyrophenones (mainly haloperidol)	—	—
Postmyocardial infarction (Dressler's syndrome)	Iodides	—	—
Pulmonary infarction	H1 and H2 blockers	—	—
Seizure disorder	Phenothiazines	—	—
Traumatic brain injury	Thyroxine	—	—

Hyperthermia

Hyperthermia is a pathophysiologic state characterized by imbalance in heat production and/or heat dissipation without disturbance in hypothalamic set point. It is caused by various infectious and noninfectious causes and include environmental toxins, heatstroke, neuroleptic malignant syndrome, malignant hyperthermia, pontine hemorrhages, and endocrine emergencies (severe thyrotoxicosis, pheochromocytoma, and adrenal crisis). This disorder need separate approach and will not be discussed further in the review.

Fever

Fever or hyperpyrexia, however, is elevated body temperature caused by upward adjustment in the thermoregulatory set point. This can also be of infectious or noninfectious origin similar to hyperthermia (Tables 1 and 2).

The pathophysiology of febrile response is not clearly understood. Fever is hypothesized as a cytokine-mediated systemic inflammatory response syndrome caused by generation of acute phase reactants and activation of autonomic, neuroendocrine, and immunological systems. Febrile response in patients with sepsis involves activation of innate immune system via toll-like receptor 4 and production of pyrogenic cytokines like interleukin (IL)-1 β , IL-6, interferon- γ , and tumor necrosis factor (TNF)- α . The pyrogenic cytokines can be exo- or endogenous; exogenous cytokines are released by macrophages in response to

TABLE 2 Infectious causes of fever in intensive care unit

Site	Possible infection
Head and neck	<ul style="list-style-type: none"> • Meningitis • Otitis media • Sinusitis • Central venous catheter-related blood stream infection
Chest	<ul style="list-style-type: none"> • Infective endocarditis • Tracheobronchitis • Healthcare/ventilator-associated pneumonia • Empyema
Abdomen and pelvis	<ul style="list-style-type: none"> • Intra-abdominal infections (e.g., spontaneous bacterial peritonitis, abscesses) • Infectious causes of diarrhea • <i>Clostridium difficile</i> infection • Infectious complications of pancreatitis • Pyelonephritis • Catheter-related urinary tract infection • Perineal or perianal abscess
Extremities	<ul style="list-style-type: none"> • Femoral line-related blood stream infection • Septic arthritis • Infected pressure sore
Skin and back	<ul style="list-style-type: none"> • Cellulitis • Infected pressure sore • Surgical site infection
Miscellaneous	<ul style="list-style-type: none"> • Postoperative fever >96 h

various stimuli.¹⁰ The pyrogenic cytokines diffuse through blood-brain barrier which then act directly on the organum vasculosum laminae terminalis in central nervous system.¹¹ The cytokines can also cause the release of prostaglandin E2 and phospholipase A2 via activation of cyclooxygenase pathway, which then bind to receptors in the hypothalamus and decrease the degree of neurons firing, resetting the thermal set point upwards. The hypothalamus then maintains homeostasis around this new set point-like normal thermoregulation causing elevated body temperature.⁴

There are negative feedback systems that prevent abnormal elevation of body temperature, e.g., glucocorticoid system, which acts via nuclear factor- κ B and/or activator protein-1 and downregulates the production of pyrogenic cytokines.⁴ The other systems which modulate febrile response are antipyretic cytokines also known as cryogens including IL-1 receptor antagonist, IL-10, and TNF- α binding protein, arginine vasopressin, and α -melanocyte stimulating hormone.¹¹ The clear understanding of interaction between antipyretics and pyrogenic cytokines is, however, still lacking. It is also not known whether the infectious and noninfectious causes induce fever through a similar molecular route.¹ There is another negative feedback mechanism, heat shock proteins (HSPs), which not only provide protection against thermal damage but also other potentially lethal stresses including hypoxia, toxins, and radiation injury. The mechanism of action of HSPs, especially HSP60 and 70, is to trigger refolding

of thermal denatured proteins and may even transport them intracellularly for degradation and elimination.¹² Heat shock proteins also directly regulates the body febrile response, e.g., inhibits pyrogenic cytokine production and programmed cell death.^{4,12}

EPIDEMIOLOGY OF FEVER IN INTENSIVE CARE UNIT

The prevalence of fever in ICU varies in different studies and ranges from 25 to 70% depending on definitions used, methods to record temperature, and etiology of fever. The important of these studies are summarized in table 3. Though a study showed incidence of fever in ICU is decreasing, still fever is one of the commonly encountered abnormal physiological variable in ICU.¹³ The significance of fever in ICU and its impact on outcome is also reported differently with either an increased risk to no difference in mortality as compared to normothermia.^{2,3,13-19} The different outcomes reported may be because of heterogeneous population studied, definition of temperature used, method of measuring temperature, and different etiology of fever. As discussed before, the etiology of fever in ICU can be divided into infectious and noninfectious origin. The new fever in ICU is mostly equated to infection despite half of the causes of fever are noninfectious.^{2,13-15} The incidence of infectious causes of fever in ICU varies from 34 to 55% (Table 2). The

TABLE 3 Epidemiology of fever in intensive care unit

Study	Patients number	Setting of ICU	Fever definition (°C)	Incidence (%)	Infectious etiology (%)	Outcome
Cicumaru et al. ¹⁴ (1999)	93		>38.4	70	53	Increased mortality among febrile patients
Barie et al. ¹⁵ (2004)	2,419	Surgical ICU	>38.2	26	46	Increased mortality among febrile patients
Peres et al. ¹⁶ (2004)	493		>38.3	28	55	Increased mortality among febrile patients
Laupland et al. ² (2008)	20,466	3 general ICU and 1 CVICU	>38.3	44	34	Only high fever (>39°C) increased mortality; OR = 1.91
Young et al. ¹⁷ (2011)	2,69,078 (ANZ) 366,973 (UK)	129 ANZ 201 UK	>39		10.8 ANZ 28.1 UK	Increased mortality without infections and decreased mortality with infections in febrile patients in the first 24 h
Laupland et al. ¹⁸ (2012)	10,962	General ICU	≥38.3	25.7		Hypothermia instead of hyperthermia was an independent predictor of death in medical patients
Lee et al. ³ (2012)	1,425	General ICU	5 ranges: • <36.5 • 36.5–37.4 • 37.5–38.4 • 38.5–39.4 • ≥39.5	0.4 23.7 46.5 21.7 7.7	42	High fever (≥39.5°C) was independently associated with mortality in nonseptic patients but not so in patients with sepsis
Niven et al. ¹ (2013)	17,153	General ICUs	≥38.3	50.1–25.5		Incidence of fever decreased from 50.1 to 25.5% over 5.5 years of the study

differentiation of infectious versus noninfectious on pattern of fever is difficult. However, some data showed the duration of fever lasting >5 days and high fever (>39.3°C) are more likely to be infectious and have higher mortality but not adjusted for illness severity, and other potential confounding factors.^{2,14} The fever in ICU almost always trigger an order set of multiple investigations to diagnose a possible infection and add to the cost of ICU stay and morbidity. The approach to the fever should be based on detailed clinical assessment including a review of the patient's history before any laboratory investigation or imaging procedures are ordered. A simplified and systematic head-to-toe approach should be used in such clinical assessment of fever. The infectious and noninfectious differential diagnoses should all be considered during assessment (Tables 1 and 2). In patients with fever and sepsis as an etiology, studies have found reduced mortality as compared to normothermia or even hypothermia.^{3,19} Conversely, in patients with a noninfectious diagnosis, higher peak temperatures were associated with an increased risk of in-hospital mortality.¹⁹

TREATMENT OF FEVER IN INTENSIVE CARE UNIT

The treatment of fever includes antipyretic drugs [paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs)] and various nonpharmacological measures. Fever has many immunophysiological effects which constitute host defense against infectious disease, e.g., like maturation of dendritic cells. The neutrophil cell motility, phagocytosis, and *in vitro* growth of intracellular bacteria in human macrophages are also shown to be enhanced by temperatures in the febrile range. The fever also enhance binding of human lymphocytes to the vascular endothelium. Few studies have suggested that suppression of febrile responses using antipyretics in patients with sepsis can be thus counterproductive and can worsen outcomes.^{3,20} Fever may have various physiological detrimental effects. In humans, fever through shivering can cause increase in oxygen consumption, minute ventilation, and metabolic rate above baseline by sixfold.^{4,21} Very high temperatures (>40°C) may worsen cerebral edema and precipitate multisystem organ failure.²² There are few negative consequences of fever reported, like the cytotoxic activity of natural killer cells is reduced by fever. High temperatures (≥41°C) may impact the function of neutrophils and macrophages negatively.³ In addition, commonly employed antipyretics (NSAIDs and/or acetaminophen) used in management of fever are associated with increased risk of bleeding, hepatic, and renal toxicity.¹ Intravenous acetaminophen has also been associated with hypotension in critically ill patients.²³ Nonpharmacological methods of fever control, like cooling blankets, ice packs, and intravascular cooling devices, can themselves increase in metabolic demand by shivering and patient discomfort. The fever being a cardinal sign of

infection, its treatment without identifying its etiology may mask the presentation and diagnosis of severe underlying infections. This, in turn, may affect the outcome of critically ill patients by delay in the administration of appropriate antimicrobial therapy. In spite of these, fever, irrespective of origin, is commonly treated in ICU with antipyretics.^{3,20}

The utility of antipyretics in ICU patients has been evaluated in a number of observational and interventional studies. The important of these studies are summarized in table 4. The data from observational studies is difficult to compare because of heterogeneity in the studies on definitions of fever, methods to record temperature, and outcome measured. In two recent observation studies with more than 15,000 patients each, again conflicting results were found.^{24,25} Suzuki et al. in their cohort found paracetamol administration appears to be independently associated with reduced in-hospital mortality across medical and surgical patients. However, in patients with suspected infection and lower illness severity using Acute Physiology and Chronic Health Evaluation (APACHE) II score, this association could not be proved.²⁴ Zhang et al. found no effect of antipyretics on mortality in ICU patients with sepsis. In fact, external cooling and not drugs were found to be harmful in patients with high fever (>39°C).²⁵ The definition of fever used was different in the two studies. Hence, it is not possible to draw any conclusion on the basis of these studies on effect of treating fever in ICU patients, especially in patients with infections.

There are many randomized trials which have been published on the evaluation of effects of antipyretics in fever treatment in ICU (Table 4). Most of these trials are, however, small in number and mainly in patients with sepsis. In a larger trial by Bernard et al., the use of ibuprofen for fever in critically ill patients with sepsis was evaluated.²⁶ Patients with severe sepsis were randomized either to receive intravenous 10 mg/kg of ibuprofen or placebo every 6 hours for a total of eight doses. This study was designed primarily to evaluate ibuprofen as an anti-inflammatory agent, hence, the study included both hypothermic and febrile patients. Although the use of ibuprofen was effective in reducing body temperature significantly, it did not alter 30-day mortality. In another open-label randomized study which included febrile ICU patients and assigned them to aggressive or permissive temperature management.²⁷ The aggressive fever control group received paracetamol 650 mg enterally every 6 hours (trigger ≥38.3°C) and physical cooling was added at higher temperature (≥39.5°C). The permissive group received paracetamol only when temperature was ≥40°C and physical cooling once it reached ≥40.5°C. Most of the patients in both the group had infectious etiology of fever. The 28-day all-cause mortality was not significantly different between the two groups. Recently, Young et al., in the largest prospective, blinded, randomized trial compared acetaminophen versus placebo for fever treatment in critically ill patients with known or suspected infection.²⁸ In the Permissive Hyperthermia Through Avoidance of Paracetamol In Known or Suspected

TABLE 4 Studies on fever treatment in intensive care unit

Study name	Design	Key findings
Observational studies		
Young et al. ¹⁷ (2011)	Cohort study in three tertiary level ICUs in Australia and New Zealand on patients with fever >38°C and known or suspected infection over a period of 6 weeks; n = 565	9% of admitted patients were included as per eligibility. Paracetamol was administered in about two-thirds of patients with fever on any given day. Physical cooling was used at least once for 12% of patients. Eligible patients have double the mortality than noneligible patients. No result on patients with paracetamol vs. non-paracetamol patients
Lee et al. ³ (2012)	Cohort study of consecutive patients admitted for >48 h to 25 ICUs in Japan and Korea; n = 1,425	High fever (≥39.5°C) was independently associated with mortality irrespective of NSAIDs or acetaminophen (antipyretics). The antipyretics use were independently associated with increased 28-day mortality in patients with sepsis but conversely, a nonsignificant trend towards a decreased mortality in patients without sepsis
Suzuki et al. ²⁴ (2015)	Multicenter retrospective observational study in 4 ICUs; n = 15,818	Out of 15,818 patients, 10,046 (64%) received at least 1 g of paracetamol. Paracetamol administration appears to be independently associated with reduced inhospital mortality across medical and surgical patients. However, paracetamol group lost statistical significance in patients with suspected infection and lower illness severity
Zhang et al. ²⁵ (2015)	Multicentric retrospective cohort, adult patients with sepsis with fever (>37.2°C); n = 15,268	There was no beneficial effect of antipyretics in reducing mortality in ICU patients with sepsis. External cooling was found harmful in patients with sepsis and high fever (>39°C)
Randomized studies		
Bernard et al. ²⁶ (1997)	Double blind placebo-controlled trial of intravenous ibuprofen treated patients with severe sepsis in seven centers in North America; n = 455	Ibuprofen significantly reduced temperature, tachycardia, oxygen consumption, and lactic acidosis in patients with sepsis. Ibuprofen, however, did not reduce the incidence or duration of shock, ARDS, and had no significant effect on 30-day mortality (37% ibuprofen-treated group vs. 40% placebo-treated group)
den Hertog et al. ³³ (2009)	Randomized blinded placebo controlled trial, acetaminophen 1 g 6 times/day or placebo in stroke patients; n = 1,400	The average temperature reduction was a modest 0.25°C in acetaminophen group. No benefit on stroke outcome was detected. In post hoc analysis, in the patients with elevated baseline temperature (37–39°C), acetaminophen appeared to improve outcome
Schortgen et al. ³² (2012)	Multicenter, randomized controlled trial of external cooling versus no cooling in patients with fever and septic shock in seven centers in France; n = 200	External cooling significantly reduced body temperature (36.8 ± 0.7 vs. 38.4 ± 1.1°C; <i>p</i> < 0.01). External cooling group had more patients with shock reversal and more patients with 50% dose reduction of vasopressors as compared to no external cooling. Day-14 mortality was significantly lower in the external cooling group but there was no significant difference in ICU or inhospital mortality between the groups
Niven et al. ²⁷ (2013)	Multicenter, unblinded randomized trial of aggressive (≥38.3°C) and vs. permissive (≥40.0°C) temperature management with acetaminophen and cooling in febrile ICU patients; n = 26	The mean daily temperature was lower in the patients in aggressive fever group. (37.8 vs. 38.0°C, <i>p</i> = 0.02). There was no significant difference in in-hospital mortality and safety outcome between the two groups
Young et al. ²⁸ (2015)	Prospective blinded trial, ICU patients with known or suspected infection; n = 700	No difference of ICU free days between the acetaminophen and the placebo group
Janz et al. ³¹ (2015)	Single-center, double-blind, placebo-controlled, severe sepsis patients; n = 40	Acetaminophen 1 g intravenous within 24 h of ICU admission may reduce oxidative injury and improve renal function in patient with severe sepsis

HEAT, Permissive Hyperthermia Through Avoidance of Paracetamol in Known or Suspected Infection in ICU; NSAIDs, nonsteroidal anti-inflammatory drugs; n, number of patients; PAIS, Paracetamol (Acetaminophen) In Stroke.

Infection In ICU [HEAT] trial, 700 ICU patients with fever (≥38°C) were randomized to receive either acetaminophen 1 g intravenous or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or

death. The primary outcome was ICU-free days (alive or discharge from ICU) from day of randomization to day 28. There was no difference in baseline characteristics of the patients between the groups, and almost all patients met

criteria for sepsis, 50–53% required vasopressors, and 57–60% required mechanical ventilation. The results showed no difference between the acetaminophen and placebo groups in the primary outcome, nor in the secondary endpoints (ICU free days, hospital-free days, ventilation-free days, inotropes-/vasopressors-free days, or need of renal replacement therapy). Similarly, there was no day 28 (13.9 vs. 13.7%, $p = 0.94$) or day 90 (15.9 vs. 16.6%, $p = 0.84$) mortality difference between the groups. There were also no discernible differences in adverse events between the groups.

The major trial on use of nonpharmacological methods in ICU patients with fever and sepsis evaluated external cooling to normothermia (36.5–37°C) for 48 hours or no external cooling.²⁹ The primary endpoint used was 50% decrease in vasopressor requirement at 48 hours after randomization. There was no significant difference between the groups for the primary endpoints. However, the study evaluated for various other secondary endpoints, like mean body temperature, the reduction in dose of vasopressor by 50% at various interval, 2 hours, 12 hours, 24 hours, and 36 hours as well as on day-14, ICU, and hospital mortality. Though day-14 mortality was noted to be significantly lower in the external cooling group (19 vs. 34%; $p = 0.0013$). This difference in mortality was not evident by the time of ICU or hospital discharge. The interpretation of the subgroup results has to be taken with caution because of possible type I error in analysis. In two published meta-analyses, author found no evidence that antipyretic therapy was either beneficial or harmful in non-neurologically injured ICU patients.^{30,31} The studies, however, included in both meta-analysis, lacked adequate statistical power, and thus, authors recommended for performing large randomized controlled trials. These meta-analysis, however, did not include recently published HEAT trial by Young et al.

To summarize, the treatment of fever in neurologically intact ICU patients with infectious etiology does not have outcome benefit from a particular treatment strategy. In neurologically intact patients, the approach to the fever is to primarily identify the source of infection and aim to remove and/or treat the source. The treatment of fever other than patient comfort has no major advantages. In noninfectious causes with higher fever ($>39.5^{\circ}\text{C}$), the fever can be controlled with antipyretics. The current studies are mainly focused on clinical outcome of fever control in ICU and will always have selection bias of appropriate source diagnosis and control. There are few studies now evaluating the biological response (cytokines, HSPs, etc.) of our temperature control strategies in patients with fever. In a recent study by Janz et al., acetaminophen 1 g given intravenously within 24 hours of ICU admission may reduce oxidative injury and improve renal function in patient with severe sepsis.³² These studies are helpful in understanding the pathophysiology of fever induction, which in turn may help clinicians to understand different temperature control strategy.

Most of the randomized trials excluded patients with neurological dysfunction (cerebrovascular accidents,

traumatic brain injury) because of reported association of poor outcome with fever in these patients.³³ In a meta-analysis, the hyperthermia demonstrated a twofold increase in short-term mortality in patients with stroke within the first 24 hours of hospitalization.³³ The recent guidelines on management of ischemic stroke also recommend the identification and treatment of hyperthermia ($>38^{\circ}\text{C}$) in patients with stroke.³⁴ The direct impact of use of antipyretics for control of fever in these patients, however, has not been evaluated properly. In a large randomized trial for evaluation of Paracetamol (Acetaminophen) In Stroke (PAIS), 1,400 patients were either assigned to acetaminophen 1 g 6 times a day or placebo.³⁵ No benefit on stroke outcome was seen, however, in a post hoc analysis in the patients with elevated baseline temperature ($37\text{--}39^{\circ}\text{C}$), treatment with acetaminophen appeared to improve outcome. Similarly, in patients with traumatic brain injury, the studies found fever as an independent predictor of poor prognosis and guidelines advocate aggressive fever control.³⁶

Hence, in patients with diagnosed or suspected neurological injury, the temperature elevation $>38^{\circ}\text{C}$ should be evaluated for any infectious causes and should be treated with antipyretics.

CONCLUSION

The current understanding of fever is still incomplete about its significance, pathophysiology and its relation to original etiology, and whether treatment is beneficial or harmful especially in patients with neurologically intact ICU patients. The approach to fever in critically ill neurological intact patients should be systematic assessment for any possible source rather than treatment of fever per se.

REFERENCES

1. Niven DJ, Léger C, Stelfox HT, et al. Fever in the critically ill: a review of epidemiology, immunology, and management. *J Intensive Care Med.* 2012;27(5):290-7.
2. Laupland KB, Shahpori R, Kirkpatrick AW, et al. Occurrence and outcome of fever in critically ill adults. *Crit Care Med.* 2008;36:1531-5.
3. Lee BH, Inui D, Suh GY, et al. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. *Crit Care.* 2012;16(1):R33.
4. Young PJ, Saxena M. Fever management in intensive care patients with infections. *Crit Care.* 2014;18(2):206.
5. Rehman T, Deboisblanc BP. Persistent fever in the ICU. *Chest.* 2014;145(1):158-65.
6. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34:730-51.
7. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med.* 2008;36(4):1330-49.
8. Schmitz T, Bair N, Falk M, et al. A comparison of five methods of temperature measurement in febrile intensive care patients. *Am J Crit Care.* 1995;4:286-92.
9. Nakamura K. Central circuitries for body temperature regulation and fever. *Am J Physiol Regul Integr Comp Physiol.* 2011;301(5):R1207-28.

10. Dinarello CA. Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. *J Endotoxin Res.* 2004;10(4):201-22.
11. Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. *Clin Infect Dis.* 2000;31 (Suppl 5):S157-61.
12. Pavlik A, Aneja IS, Lexa J, et al. Identification of cerebral neurons and glial cell types inducing heat shock protein Hsp70 following heat stress in the rat. *Brain Res.* 2003;973(2):179-89.
13. Niven DJ, Stelfox HT, Shahpori R, et al. Fever in adult ICUs: An interrupted time series analysis. *Crit Care Med.* 2013;41:1863-9.
14. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med.* 1999;25:668-73.
15. Peres Bota D, Lopes Ferreira F, Melot C, et al. Body temperature alterations in the critically ill. *Intensive Care Med.* 2004;30:811-6.
16. Barie PS, Hydo LJ, Eachempati SR. Causes and consequences of fever complicating critical surgical illness. *Surg Infect (Larchmt).* 2004;5:145-59.
17. Young P, Saxena M, Eastwood GM, et al. Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study. *Crit Care Med.* 2011;13:97-102.
18. Laupland KB, Zahar JR, Adrie C, et al. Determinants of temperature abnormalities and influence on outcome of critical illness. *Crit Care Med.* 2012;40:145-51.
19. Young PJ, Saxena M, Beasley R, et al. Early peak temperature and mortality in critically ill patients with or without infection. *Intensive Care Med.* 2012;38:437-44.
20. Fumagalli R, Bellani G, Perri A. Which drugs for the control of fever in critical patients. *Curr Drug Targets.* 2009;10(9):881-6.
21. Manthous CA, Hall JB, Olson D, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med.* 1995;151(1):10-4.
22. Cremer OL, Kalkman CJ. Cerebral pathophysiology and clinical neurology of hyperthermia in humans. *Prog Brain Res.* 2007;162:153-69.
23. Krajová A, Matoušek V, Duška F. Mechanism of paracetamol-induced hypotension in critically ill patients: a prospective observational cross-over study. *Aust Crit Care.* 2013;26(3):136-41.
24. Suzuki S, Eastwood GM, Bailey M, et al. Paracetamol therapy and outcome of critically ill patients: a multicenter retrospective observational study. *Crit Care.* 2015;19:162.
25. Zhang Z, Chen L, Ni H. Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature. *PLoS One.* 2015;10(3):e0121919.
26. Bernard GR, Wheeler AP, Russell JA, et al. The Ibuprofen in Sepsis Study Group. The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med.* 1997;336:912-8.
27. Niven DJ, Stelfox HT, Leger C, et al. Assessment of the safety and feasibility of administering antipyretic therapy in critically ill adults: A pilot randomized clinical trial. *J Crit Care.* 2013;28:296-302.
28. Young P, Saxena M, Bellomo R, et al. Acetaminophen for fever in critically ill patients with suspected infection. *N Engl J Med.* 2015;373(23):2215-24.
29. Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. *Am J Respir Crit Care Med.* 2012;185:1088-95.
30. Jefferies S, Weatherall M, Young P, et al. The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis. *Crit Care Resusc.* 2011;13(2):125-31.
31. Greer DM, Funk SE, Reaven NL, et al. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. *Stroke.* 2008;39(11):3029-35.
32. Janz DR, Bastarache JA, Rice TW, et al. Randomized, placebo-controlled trial of acetaminophen for the reduction of oxidative injury in severe sepsis: the Acetaminophen for the Reduction of Oxidative Injury in Severe Sepsis trial. *Crit Care Med.* 2015;43(3):534-41.
33. Prasad K, Krishnan PR. Fever is associated with doubling of odds of short-term mortality in ischemic stroke: an updated meta-analysis. *Acta Neurol Scand.* 2010;122:404-8.
34. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013;44(3):870-947.
35. den Hertog HM, van der Worp HB, van Gemert HM, et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol.* 2009;8:434-40.
36. Bao L, Chen D, Ding L, et al. Fever burden is an independent predictor for prognosis of traumatic brain injury. *PLoS One.* 2014;9(3):e90956.

Section 5

Nephrology

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Perioperative Dysnatremia

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INTRODUCTION

Disorders of plasma sodium concentration are commonly encountered in hospitalized patients and have been associated with an increased length-of-stay, increased resource utilization, and mortality.^{1,2} Hyponatremia is particularly common and has significant consequences in a range of clinical conditions despite being potentially reversible.^{1,3} The incidence of adverse outcomes has also been postulated to occur in patients with either asymptomatic or particularly mild hyponatremia.¹ The clinical effects of dysnatremia are particularly apparent in the surgical population as the perioperative period is known to be associated with significant fluid losses, varying fluid replacement regimes, and then, endocrine surgical stress response.³ Studies published in the literature have previously explored hospital outcomes of dysnatremia present on admission or in specific medical or surgical specialties. However, recently, there has been an emerging interest in the incidence and outcomes of dysnatremia in the perioperative period and the changes in sodium plasma concentration during this time. Although small changes in sodium concentration may be expected secondary to either diurnal variation or measurement artifact, larger changes often relate to endocrine or iatrogenic factor.^{4,5} These changes can often be rapid leading to osmotic disturbances or cerebral dysfunction resulting in adverse perioperative outcomes.

This review will briefly focus on the physiology of sodium homeostasis and the common dysnatremias encountered in the perioperative period. It will then review the implications and complications of perioperative dysnatremia.

SODIUM HOMEOSTASIS

Sodium is the most abundant ion in the extracellular fluid and along with chloride and bicarbonate, contributes approximately 90% of the extracellular osmolality.⁶ As a result, the regulation of plasma osmolality is intimately

correlated with the plasma sodium concentration. Under normal physiological conditions, normal concentrations are maintained within a tight range of between 138 and 142 mmol/L, although values between 135 and 145 mmol/L are generally considered normal.⁷

In healthy adult physiology, fluctuations of sodium concentration and total body water are minimal despite activities such as ingestion of large volumes of water or strenuous exercise.

Numerous systems control the fine balance but thirst, antidiuretic hormone (ADH), and aldosterone are the most important regulators of plasma concentration. The plasma water content is the main determinant of sodium concentration and this in itself is affected by water intake, insensible losses and urinary dilution.⁸ In response to an increase in extracellular fluid osmolality, ADH is released from the posterior pituitary which acts on the cortical collecting tubules and collecting ducts. The permeability of the aforementioned structures thereby increases leading to an increase in water reabsorption and consequently, concentrated urine. This serves to rid the body of excess sodium while relatively preserving water. Extracellular fluid is "diluted", thereby normalizing the plasma concentration. The exact opposite occurs when the plasma becomes hypo-osmotic. Less ADH is produced, which allows larger volumes of diluted urine to be excreted.

Disorders of sodium imbalance can be broadly classified into hypo- and hypernatremia. Hyponatremia is defined as a plasma sodium of <135 mmol/L and the causes can be broadly classified clinically according to the patient's extracellular fluid volume status, e.g., hypervolemic, hypovolemic, or euvolemic. Hyponatremia is more commonly encountered in the perioperative period and can be secondary to a combination of pathological and iatrogenic factors. In the perioperative setting, it is usually a reflection of excess water relative to sodium, which is commonly due to dilution of sodium by either fluid overload or depletion of total body sodium in excess of body water losses.⁸ The symptoms of

hyponatremia are related to both the severity and how rapidly the plasma concentration falls. Mild hyponatremia is usually asymptomatic with symptoms such as nausea and malaise starting at concentrations between 125 and 130 mmol/L. Severe and rapidly occurring hyponatremia can result in seizures, respiratory arrest, brainstem herniation, and death.⁸

Hypernatremia is defined as a sodium level over 150 mmol/L and is much less common than hyponatremia. Symptoms are usually only evident when plasma concentrations rise to between 158 and 160 mmol/L. The cause of this is primarily due to water loss (either pure water or hypotonic fluid).

PERIOPERATIVE INCIDENCE AND IMPLICATIONS OF DYSNATREMIA

Perioperative dysnatremias are a common finding in the surgical population with a recent study published in 2016 demonstrating that 23.8% of patients in the preoperative setting were hyponatremic (serum sodium <137 mmol/L) and 14.9% were hypernatremic (serum-sodium >143 mmol/L).⁶ This study was a secondary analysis of the European Surgical Outcomes Study (EuSOS), which analyzed the data of over 46,000 patients presenting for elective noncardiac surgery. The results also found that patients with dysnatremia were more likely to be undergoing emergency surgery and to have associated comorbidities. Dysnatremia was found to be twice as common in patients with cirrhosis, congestive heart failure, or coronary heart disease compared to those who did not have those comorbidities. Hyponatremia was also found to occur more frequently in patients with chronic obstructive pulmonary disease.⁶ The most significant finding of the study was that although perioperative dysnatremia is significantly associated with mortality, only severe hypernatremia is independently associated with an increased risk of death. The results of the analysis showed that after adjustment for confounding factors, a more than threefold increase in mortality was found for patients presenting with a serum-sodium of >149 mmol/L [odds ratio (OR) 3.42]. Postulated explanations for this include the possibility that these patients were either dehydrated or exposed to more significant fluid and electrolyte shifts during the perioperative period.⁶ Hypernatremia itself can also lead to reduced cardiac contractility and decreased peripheral insulin resistance and it is possible that these also played a role in the increased mortality observed.⁶ The fact that only severe hypernatremia was independently associated with mortality is an interesting finding as it is in contrast to previous studies, which have found an independent association with morbidity and mortality with both hyponatremia and hypernatremia. In 2012, Leung et al. published their results of a cohort study using over 75,000 patients from the National Surgical Quality Improvement Pathway database. They found that preoperative hyponatremia was associated with an increased risk of 30-day mortality (5.2 vs. 1.3%, adjusted

OR 1.44, confidence interval 1.38–1.50) and this was most significant in patients undergoing nonemergency surgery and in American Society of Anesthesiologists class 1 or 2.⁹ In this study, hyponatremia was also found to be associated with a greater risk of major postoperative coronary events, wound infections, pneumonia, and prolonged length-of-stay. A study by the same authors published the following year using the same database also found that preoperative hypernatremia is associated with increased perioperative 30-day morbidity and mortality.¹⁰ Even mild degrees of dysnatremia have been linked to adverse outcomes and this was confirmed in a larger study, which concluded that dysnatremia, which included mild changes in serum-sodium concentration, was an independent risk factor for hospital mortality.^{11,12} As previously discussed, ADH plays an important role in the regulation of sodium homeostasis and it is well-known that the surgical stress response triggered postoperatively can lead to an increase in ADH. In addition, ADH release is triggered by pain, nausea, vomiting, and volume depletion, which are all factors that commonly occur in the perioperative period. Interestingly, however, Waikar et al. demonstrated that the association between mortality and hyponatremia was independent of ADH activity.^{6,13} The causes of hyponatremia, perioperatively, are multifactorial and as Cecconi et al. suggested, it is likely that the underlying cause of the sodium imbalance is of greater significance than the numerical value itself.

Although we have discussed the perioperative effects of dysnatremia, we must question what are the preoperative implications of these findings? Although there is no strong evidence at present to suggest that the sodium should be corrected prior to surgery, the preoperative finding of dysnatremia should alert clinicians to the increased perioperative risk and should prompt clinicians to investigate the possibility of underlying disease, which may be responsible.⁶ The authors of the secondary analysis of the EuSOS study also suggest that preoperative sodium concentration could be used to stratify perioperative mortality.⁶ However, in order for this to be effective, increased awareness of the adverse effects of dysnatremia is required and further research is warranted to determine whether correction of sodium in the preoperative period can lead to reduced perioperative morbidity and mortality.

CONCLUSION

Dysnatremia is commonly encountered in the perioperative period and research has demonstrated that both hyponatremia and hypernatremia are associated with adverse postoperative outcomes. Measurement of serum-sodium concentration is a rapid, simple and inexpensive and it has been suggested that it could be used to potentially stratify perioperative risk. At present, there is a lack of evidence to recommend correction of sodium preoperatively, but further research in this area is warranted.

REFERENCES

1. Leung AA, McAlister FA, Rogers SO, et al. Preoperative hyponatremia and perioperative complications. *Arch Intern Med.* 2012;172:1474-81.
2. Leung AA, McAlister FA, Finlayson SRG, et al. Preoperative hypernatremia predicts increased perioperative morbidity and mortality. *Am J Med.* 2013;126:877-86.
3. Upadhyay A, Jabias BL, Madias NE. Epidemiology of hyponatraemia. *Semin Nephrol.* 2009;29:227-38.
4. Lacher DA, Hughes JP, Carroll MD. Biological variation of laboratory analytes based on the 1999-2002 National Health and Nutrition examination survey. *Natl Health Stat Report.* 2010;21:1-7.
5. Cecconi M, Hochrieser H, Chew M, et al. Preoperative abnormalities in serum sodium concentration are associated with higher in-hospital mortality in patients undergoing major surgery. *BJA.* 2016;116:63-9.
6. Sterns RH. Disorders of plasma sodium—causes, consequences and correction. *N Engl J Med.* 2015;372:55-65.
7. Reynolds RM, Padfield PH. Disorders of sodium balance. *BMJ.* 2006;332:702-5.
8. Leung AA, McAlister FA, Rogers SO Jr, et al. Preoperative hyponatremia and perioperative complications. *Arch Intern Med.* 2012;172:1474-81.
9. Leung AA, McAlister FA, Finlayson SRG, et al. Preoperative hypernatremia predicts increased perioperative morbidity and mortality. *Am J Med.* 2013;126:877-86.
10. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatraemias present on ICU admission. *Intensive Care Med.* 2010;36:304-11.
11. Darmon M, Diconne E, Souweine B, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. *Crit Care.* 2013;17:R12.
12. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance haemodialysis. *Am J Med.* 2011;124:77-84.

Hypophosphatemia in Intensive Care Unit

Jayant R Shelgaonkar

INTRODUCTION

Electrolyte abnormalities are frequently seen in the critically ill patients during the course of their stay in the intensive care unit (ICU) patients. Hypophosphatemia is frequently seen in these patients and its presence is associated with significant morbidity. The prevalence of hypophosphatemia is about 28% in critically ill patients.¹

NORMAL PHOSPHATE HOMEOSTASIS

Phosphorus is an essential element for all living cells with various functions (Table 1).² The phosphate balance is a complex interplay between phosphate uptake and phosphate excretion. Normal values of the total serum phosphate level are 0.80–1.45 mmol/L (2.5–4.5 mg/dL).

The phosphate found in the blood exists in two forms—(i) organic and (ii) inorganic form, with a total (organic + inorganic) constituting plasma concentration of 3.9 mmol/L. The organic form comprises mainly phospholipids and accounts for approximately two-thirds of the total. The

inorganic form comprises the remainder and is the quantity normally measured by standard laboratory tests. This is made up of free inorganic phosphate (85%), which exists as a combination of HPO_4^{2-} , H_2PO_4^- , and PO_4^{3-} ions. The ratio of these ions depend on plasma acid-base balance.¹

The normal dietary intake of phosphate is 1,200 mg/day in the adult. The homeostasis of phosphate is controlled by parathyroid hormone, 1,25-dihydroxycholecalciferol and calcitonin and three main organs—the intestine, the kidneys, and bone.

Uptake of phosphate occurs along the length of the intestinal tract with the jejunum being the main site of absorption. It is thought that there are two mechanisms of phosphate absorption. The first is a sodium-dependent active transport mechanism in the proximal intestine,³ which can be blocked by diphosphonates and calcitonin⁴ and enhanced by 1,25-dihydroxycholecalciferol. This process is directly related to the intraluminal sodium concentration. The second involves the passive diffusion of phosphate ions, mainly from the jejunum⁵ and ileum.³ This mechanism is related to the concentration of phosphate, so that when the dietary intake of phosphate is low, the first mechanism predominates. Gut absorption is affected directly by calcium ions, which bind intraluminal phosphate, forming insoluble complexes and thus decreasing the bioavailability of both ions.⁶ The phosphate is also secreted into the gastrointestinal tract, mainly in saliva and bile acids. Approximately 60% of the secretion is reabsorbed.⁷

The main regulatory organ for phosphate is the kidney. In a normal, healthy human, renal phosphate excretion matches net intestinal absorption, thereby achieving a zero balance. The glomerulus filters 90% of the phosphate passively. Reabsorption is an active carrier-mediated process, which occurs mainly in the proximal tubule and is influenced by urinary pH. The main regulators are parathyroid hormone, which decreases tubular absorption and hyperphosphatemia, which, along with respiratory and metabolic acidosis enhances urinary losses.

TABLE 1 Functions of phosphate

Form	Function
Hydroxyapatite	Bone structure
Phospholipids	Structure of cell membrane
Adenosine triphosphate and creatinine phosphate	Energy storage and metabolism
Nucleic acid and nucleoproteins	Genetic translation
Phosphorylation of proteins	Key regulatory mechanism; activation of enzymes, cell-signaling cascade
2,3-Diphosphoglycerate	Modulates oxygen release by hemoglobin
Inorganic phosphate	Acid-base buffer

TABLE 2 Common causes of hypophosphatemia

Decreased intestinal absorption	Intestinal redistribution	Increased renal excretion
<ul style="list-style-type: none"> • Malnutrition • Phosphate-binding agents • Vitamin D deficiency/resistance • Secretory diarrhea • Steatorrhea • Vomiting • Nasogastric suctioning 	<ul style="list-style-type: none"> • Respiratory alkalosis • Recovery from malnutrition • Recovery from diabetic ketoacidosis • Glucose/insulin therapy • Catecholamines • Rapid cell uptake/proliferation (e.g., hungry bone syndrome and acute leukemia) 	<ul style="list-style-type: none"> • Increased renal excretion • Metabolic acidosis • Diuretics • Volume expansion • Corticosteroids • Tubular disorders • Hereditary syndromes • Hyperparathyroidism • Malignancy-induced hypophosphatemia
Causes in the critically ill		
<ul style="list-style-type: none"> • Sepsis • Postoperative state • Trauma • Fluid therapy • Refeeding • Acid-base disorders <ul style="list-style-type: none"> ◦ Metabolic acidosis ◦ Respiratory alkalosis 	<ul style="list-style-type: none"> • Medication <ul style="list-style-type: none"> ◦ Glucose/insulin therapy ◦ Catecholamines ◦ Diuretics • Renal replacement therapy 	

Hypophosphatemia can be caused by three different mechanisms (Table 2):^{8,9}

- Decreased intestinal absorption
- Internal redistribution of inorganic phosphate
- Increased renal excretion.

In most patients with severe hypophosphatemia, both depletion of total body phosphorus stores and redistribution of phosphate to the intracellular space are found.

- Decreased intestinal absorption of phosphate rarely causes hypophosphatemia, as a low-phosphate diet increases renal reabsorption and enhances intestinal uptake of phosphate. Still, malnutrition, diarrhea, and nasogastric suction-causing hypophosphatemia are common features in critically ill patients
- Redistribution across the cell membrane is the most common cause of hypophosphatemia in ICU patients and can be caused by multiple clinical conditions.⁸ Respiratory alkalosis-induced increase of intracellular pH causes phosphate to enter the cell by stimulating glycolysis, administration of glucose and insulin also stimulates carbohydrate metabolism, during which phosphate is transported into the cells along with glucose; high serum levels of catecholamines such as epinephrine and norepinephrine, whether endogenous or exogenous, cause a decrease in serum phosphate.¹⁰ Cellular uptake of phosphate is increased under certain specific conditions such as the refeeding syndrome, hungry-bone syndrome and diseases with rapid cell proliferation such as acute leukemia
- Renal excretion of phosphate is increased by metabolic acidosis and by many drugs, including diuretics, glucocorticoids,¹¹ aminoglycosides, antiretroviral drugs, and anticancer drugs.

Hypophosphatemia can be found in patients with severe infections, such as sepsis, particularly in patients with Gram-negative bacteremia.¹² Hypophosphatemia often develops in the postoperative phase.¹³ Multiple causal factors may be present, such as respiratory alkalosis, administration of insulin, and the use of diuretics. This is particularly true for major surgery such as cardiac surgery and abdominal aortic surgery. After major hepatic surgery, hypophosphatemia is extremely frequent. Reported mechanisms involve both shifts of phosphate into hepatocytes¹⁴ and renal phosphate wasting.¹⁵ In trauma patients, hypophosphatemia is seen because of altered renal phosphate handling resulting in increased urinary phosphate excretion.¹⁶ In burn patients, hypophosphatemia is frequently seen because of phosphate loss through the skin.¹⁷ In patients with malnutrition, a so-called refeeding syndrome may develop when they receive enteral feeding, a syndrome characterized by multiple metabolic abnormalities including depletion of total body phosphorus stores and redistribution of phosphate to the intracellular compartment, which may result in severe hypophosphatemia.¹⁸ Hypothermia induces diuresis and is associated with hypophosphatemia as well.¹⁹ The use of continuous renal replacement therapy may lead to hypophosphatemia when low-phosphate replacement solution and dialysate are used. Patients who require high-flux dialysis for intoxications are especially at risk. Addition of potassium phosphate to dialysate and replacement fluids safely prevent the development of hypophosphatemia.²⁰ Finally, patients with diabetic ketoacidosis commonly present with hypophosphatemia due to increased urinary phosphate excretion. Phosphate levels generally decrease further during treatment because of intracellular shifting along with glucose and potassium.²¹

EPIDEMIOLOGY OF HYPOPHOSPHATEMIA

Hypophosphatemia is categorized as moderate [serum phosphate level of 0.32–0.65 mmol/L (1–2 mg/dL)] or severe (<0.32 mmol/L (<1 mg/dL)). In the general hospital population, the prevalence of moderate hypophosphatemia ranges between 2.2 and 3.1%, and the prevalence of severe hypophosphatemia is reported to be 0.2–0.4%.^{22,23} One study reports 45% of all hypophosphatemia cases occur in hospital population.²⁴ Hypophosphatemia has high incidence in certain patients groups, such as sepsis and diabetic ketoacidosis. In postoperative patients, such as elective cardiac surgery, the incidence is around 34%. It is very common after major hepatic surgery in the first postoperative week. Trauma patients also have high incidence of hypophosphatemia especially in patients with burn wounds and head trauma.^{25,26}

CLINICAL SYMPTOMS (BOX 1)

Hypophosphatemia causes impaired energy metabolism, which leads to cellular dysfunction in multiple organ systems.

MANAGEMENT OF HYPOPHOSPHATEMIA

Due to high prevalence of hypophosphatemia in critically ill patients, especially in the high-risk groups, frequent laboratory monitoring is recommended.²⁷ Although it is recommended to correct hypophosphatemia in patients with symptoms, there is no randomized controlled evidence to indicate whether correction of hypophosphatemia leads to improved outcome.

Box 1: Symptoms of hypophosphatemia²⁷

- | | |
|---|----------------------------|
| • Respiratory | • Hematologic |
| ◦ Respiratory muscle dysfunction | ◦ Hemolysis |
| – Acute respiratory failure | ◦ Leukocyte dysfunction |
| – Failure to wean from mechanical ventilation | • Endocrine |
| ◦ Decreased peripheral oxygen delivery | ◦ Insulin resistance |
| • Cardiovascular | • Neuromuscular |
| ◦ Decreased myocardial contractility | ◦ Skeletal muscle weakness |
| ◦ Acute heart failure | ◦ Rhabdomyolysis |
| ◦ Increased inotropic requirement | ◦ Polyneuropathy |
| ◦ Arrhythmia | ◦ Altered mental status |
| – Ventricular tachycardia | ◦ Seizures |
| – Supraventricular tachycardia | |
| – Premature beats | |

Hypophosphatemia can be corrected orally as well as intravenously. Intravenous administration is associated with complications like precipitation with calcium, large intravenous doses of phosphate can lead to hyperphosphatemia, hypomagnesemia, hypocalcemia, and hypotension. Therefore, intravenous administration is recommended for patients with symptomatic hypophosphatemia and phosphate levels less than 0.32 mmol/L. Multiple studies have evaluated the efficacy and safety of intravenous phosphate supplementation. These studies generally agree that aggressive phosphate supplementation is safe with phosphate doses up to 45 mmol with infusion rates up to 20 mmol/h. In patients with potassium levels more than 4 mmol/L, sodium phosphate instead of potassium phosphate is recommended. One study calculated total phosphate replacement dose based on the actual serum phosphate levels in mmol/L, a target level of 1.25 mmol/L and a phosphate distribution volume of 0.5 L/kg body weight.

$$\text{Phosphate dose} = 0.5 \times (\text{body weight}) \times [1.25 - (\text{serum phosphate})]$$

Body weight in kilogram, serum phosphate in millimoles per liter, and phosphate dose in millimoles.²⁸

Moderate hypophosphatemia can be treated with oral supplementation of phosphate. Supplementation of active vitamin D is required for intestinal absorption of phosphate. Typical oral supplementation amounts are three times the normal daily intake, with advised amounts of 2.5–3.5 grams (80–110 mmol) per day, divided over two to three doses. Patients, who receive feeding after a period of starvation are often phosphate depleted, so additional phosphate should be added to nutritional preparations. An additional preventive strategy is to build up the caloric intake slowly.²⁹ The total required amount of phosphate cannot be predicted by serum phosphate levels, as phosphate shifts between multiple body compartments. Dipyridamole can decrease urinary phosphate loss.³⁰ Further research is needed to establish further the role of this drug in the treatment of hypophosphatemia in critically ill patients.

CONCLUSION

The incidence of hypophosphatemia in ICU depends on the underlying cause. There are three major mechanisms by which hypophosphatemia can occur: (i) decreased intestinal absorption, (ii) internal redistribution, and (iii) increased urinary loss. There is often a combination of factors responsible for hypophosphatemia. Because of internal shifts, hypophosphatemia does not necessarily mean phosphate depletion. Lack of phosphate can lead to tissue hypoxia and disruption of cellular function. The identification and treatment of primary cause usually lead to normalization of the plasma phosphate levels.

REFERENCES

- Bugg NC, Jones JA. Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. *Anaesthesia*. 1998;53(9):895-902.
- Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;118(10):1094-101.
- Danisi G, Straub RW. Unidirectional influx of phosphate across the mucosal membrane of rabbit small intestine. *Pflugers Archiv*. 1980;385(2):117-22.
- Juan D, Liptak P, Gray TK. Absorption of inorganic phosphate in the human jejunum and its inhibition by salmon calcitonin. *J Clin Endocrinol Metab*. 1976;43(3):517-22.
- Walling MW. Intestinal inorganic phosphate transport. *Adv Exp Med Biol*. 1978;103:131-47.
- Clark I. Importance of dietary ca:PO₄ ratios on skeletal Ca, mg and PO₄ metabolism. *Am J Physiol*. 1969;217(3):865-70.
- Wilkinson R. Absorption of calcium, phosphorous and magnesium. In: BEC Nordin (Eds). *Calcium, Phosphate and Magnesium metabolism*. London: Churchill Livingstone; 1976. Pp. 36-112.
- Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;118(10):1094-101.
- Amanzadeh J, Reilly RF Jr. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nat Clin Pract Nephrol*. 2006;2(3):136-48.
- Kjeldsen SE, Moan A, Petrin J, et al. Effects of increased arterial epinephrine on insulin, glucose and phosphate. *Blood Press*. 1996;5(1):27-31.
- Murer H, Hemando N, Forster I, et al. Proximal tubular phosphate reabsorption: molecular mechanisms. *Physiol Rev*. 2000;80(4):1373-409.
- Riedler GF, Scheitlin WA. Hypophosphataemia in septicaemia: higher incidence in gram-negative than in gram-positive infections. *Br Med J*. 1969;1(5646):753-6.
- Goldstein J, Vincent JL, Leclerc JL, et al. Hypophosphatemia after cardiothoracic surgery. *Intensive Care Med*. 1985;11(3):144-8.
- George R, Shiu MH. Hypophosphatemia after major hepatic resection. *Surgery*. 1992;111(3):281-6.
- Salem RR, Tray K. Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. *Ann Surg*. 2005;241(2):343-8.
- Daily WH, Tonnesen AS, Allen SJ. Hypophosphatemia: incidence, etiology, and prevention in the trauma patient. *Crit Care Med*. 1990;18(11):1210-4.
- Berger MM, Rothen C, Cavadini C, et al. Exudative mineral losses after serious burns: a clue to the alterations of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65(5):1473-81.
- Marinella MA. Refeeding syndrome and hypophosphatemia. *J Intensive Care Med*. 2005;20(3):155-9.
- Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. *J Neurosurg*. 2001;94(5):697-705.
- Troyanov S, Geadah D, Ghannoum M, et al. Phosphate addition to hemodiafiltration solutions during continuous renal replacement therapy. *Intensive Care Med*. 2004;30(8):1662-5.
- English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J*. 2004;80(943):253-61.
- Larsson L, Rebel K, Sorbo B. Severe hypophosphatemia: a hospital survey. *Acta Med Scand*. 1983;214(3):221-3.
- King AL, Sica DA, Miller G, et al. Severe hypophosphatemia in a general hospital population. *South Med J*. 1987;80(7):831-5.
- Hoffmann M, Zemlin AE, Meyer WP, et al. Hypophosphataemia at a large academic hospital in South Africa. *J Clin Pathol*. 2008;61(10):1104-7.
- Berger MM, Rothen C, Cavadini C, et al. Exudative mineral losses after serious burns: a clue to the alterations of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65(5):1473-81.
- Polderman KH, Bloemers FW, Peerdeman SM, et al. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med*. 2000;28:2022-5.
- Geerse DA, Bindels AJ, Kuiper MA, et al. Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care*. 2010;14(4):R147.
- Bech A, Blans M, Raaijmakers M, et al. Hypophosphatemia on the intensive care unit: Individualised phosphate replacement based on the serum levels and distribution volume. *J Crit Care*. 2013;28(5):838-43.
- Marinella MA. Refeeding syndrome and hypophosphatemia. *J Intensive Care Med*. 2005;20(3):155-9.
- Prie D, Blanchet FB, Essig M, et al. Dipyrindamole decreases renal phosphate leak and augments serum phosphorus in patients with low renal phosphate threshold. *J Am Soc Nephrol*. 1998;9(7):1264-9.

Anticoagulation: The Various Options in Renal Replacement Therapy

Khusrav B Bajan

INTRODUCTION^{1,2}

Renal replacement therapy (RRT) is a modality of extracorporeal circulation offered to the critically ill patients with acute kidney injury or to the relatively stable chronic renal failure patients. Kidney disease is beset with disturbances in the coagulation system, such as dysfunctional platelets, making the decision on the use of anticoagulation in this scenario even more challenging and complex. Trying to maintain patency of the extracorporeal circuit during RRT using anticoagulation, one often lands up with dreaded complications such as intracranial hemorrhage and major gastrointestinal bleed. We, thus, would make an attempt, in this chapter to touch upon some controversial yet key issues such as optimization and individualization of anticoagulation in the hemodialysis setting, options to reduce complications of systemic heparinization, and to find out nonanticoagulation based strategies to prevent complications.

RECOMMENDATIONS³⁻¹⁰

Various organizations and nephrology societies, such as the Canadian Society of Nephrology, Caring for Australians with Renal Impairment, National Kidney Foundation, European Best Practice Guidelines, and the British Renal Association, have made various recommendations on:

- Adequacy of anticoagulation to achieve optimal dialysis
- Difference between unfractionated heparin (UFH) and low molecular weight heparin (LMWH)
- Dosage of heparin during dialysis
- Use of citrate and saline infusion in the dialysis setting.

The heterogeneity on these controversial issues highlights the need for newer and appropriate consensus guidelines.

OPTIONS TO REDUCE SYSTEMIC HEPARINIZATION

In patients at risk for bleeding due to systemic anticoagulation, such as heparin induced thrombocytopenia (HIT) syndrome and previous use of antiplatelets and anticoagulants; various modalities, such as regional anticoagulation, low dose heparin rinsing of circuit, saline boluses, and the use of synthetic membrane dialysis with an affinity for heparin, have been used to maintain filter patency.

Regional Anticoagulation¹¹⁻¹³

The use of protamine to neutralize the anticoagulant effect of systemic heparin has been complex, ineffective, and hence, abandoned in favor of other safer strategies. A safer use of prostacyclin, an endogenous prostaglandin with its antiaggregatory effect on platelets, is an option for regional anticoagulation. However, its use has been limited on account of complications, such as hypotension and systemic flushing due to vasodilatory properties, and its high cost. Regional anticoagulation using citrate due to its inherent properties of chelating calcium and thus blocking the coagulation cascade is a popular option. Citrate toxicity could lead to metabolic alkalosis after being metabolized to bicarbonate and also lead to metabolic acidosis if for some reason not metabolized. The use of citrate needs cautious monitoring of ionized calcium and is very costly and complex, and hence, has not stood the test of time.

Anticoagulation-free Dialysis¹⁴⁻¹⁶

Frequent saline flushes of 100–200 mL half hourly or a continuous saline infusion (200 mL/h) could be an

alternative practice to prevent filter clotting. This strategy has not been proven in studies to reduce the filter clotting episodes substantially and is also labor intensive. A single-center randomized controlled nonblinded study including 50 heparin-free dialysis, showed 24% of filter clotting with continuous saline infusion as against 48% filters clotting when intermittent saline boluses were used ($p = 0.04$). In contrast to this, a post hoc analysis HepZero study showed that saline flushes achieve higher success than the predilution continuous saline method.

Role of Heparin-coated Dialysis Membranes in Low Dose Heparin or Heparin-free Dialysis¹⁷⁻²⁰

Heparin rinse of the circuit has been used as an alternative technique to prevent filter clotting for many years, but in vain. Few studies have shown some benefit of heparin rinse, if used along with commercially available dialysis membranes, such as hemophan, AN69ST, and HeprAN, that allows adsorption of heparin through the blood contacting surface of the membrane. A study using hemophan filter, though showing a 15-minute increase in the activated partial thromboplastin time after initiation of dialysis, had a 7% occurrence of severe clotting. A clinical study comparing three modalities; low dose heparin, AN69ST, and other high flux membranes, such as polysulfones, in heparin-free dialysis; failed to show any significant difference. A Reduction of Heparin dose in Dialysis with Evodial System (RHODES) study using HeprAN, (polyacrylonitrile membrane with a heparin graft) adopted a stepwise reduction in the regular heparin dose (UFH or LMWH) in 45 hemodialysis patients until signs of clotting were observed. It showed a 50% decrease in the anti-Xa activity and a 67% reduction in the heparin dose required. A HepZero study including 251 heparin-free hemodialysis patients showed a success rate with the use of heparin-grafted membranes as compared to current standard of care strategies of saline boluses (68.5 vs. 50.4%; $p = 0.003$).

Alternative Anticoagulants to Heparin²¹⁻²⁵

New anticoagulants that can either directly inhibit thrombin or slow down thrombin generation by blocking factor Xa have been recently developed for use, especially to prevent HIT in dialysis patients.

Danaparoid, a mixture of glycosaminoglycans with a predominant anti-Xa activity (anti-Xa over anti-IIa ratio) has been used in patients requiring dialysis to prevent HIT.

Fondaparinux, a Xa inhibitor, not licensed for use in HIT, has been tried in dialysis patients.

Some direct and indirect thrombin inhibitor, such as lepirudin, hirudin, bivalirudin, dermatan sulfate, and argatroban, have been proposed to achieve safe anticoagulation during dialysis of HIT patients. In patients with high risk of bleeding, a study conducted comparing use of low dose argatroban into saline flushes with plain heparin-

free hemodialysis sessions showed a good efficiency in preventing filter clotting.

Some newer oral anticoagulants, such as rivaroxaban, dabigatran, and apixaban, have yet to be studied in the setting of hemodialysis for their efficacy and safety profile.

INDIVIDUALIZATION OF ANTICOAGULATION THERAPY

Anticoagulation in RRT is challenging and needs to be individualized, thus the need to look into individual patient profiles defining them into high or low risk for bleeding.

Patients at High Risk for Bleeding²⁶⁻²⁹

The following patients are at high risk for bleeding:

- A recent cranial trauma
- Perioperative phase
- Gastric ulcers
- Esophageal varices
- Intercurrent infections
- Medication history, especially of nonsteroidal anti-inflammatory drugs and steroids.

In addition, a Dialysis Outcomes and Practice Patterns Study (DOPPS) denoted that a history of gastrointestinal bleeding in the last 12 months was strongly predictive of a major bleeding event whilst on dialysis therapy.

Patients Requiring Antithrombotic Therapy

The use of antithrombotic agents, such as oral anticoagulants and antiplatelet agents, in dialysis patients for the prevention of life-threatening complications, such as stroke, venous thromboembolism, myocardial infarction, and major cardiovascular events, has been the mainstay modality.

Oral Anticoagulants³⁰⁻³⁴

Atrial fibrillation is common (prevalence 7-27%) with a 10- to 20-fold higher incidence in elderly patients. In order to prevent strokes, patients with atrial fibrillation are usually on warfarin or any other anticoagulants. Studies have shown that dialysis patients who have received warfarin have a 2-fold higher risk of bleeding than those not receiving anticoagulants. In the same studies, these patients were also noted to have a 3- to 10-fold increased occurrence of bleeding than those on warfarin without dialysis. The incidence of major bleeding episodes in dialysis patients without warfarin exposure was found to be 2.5% per person-year as compared to 3.1% for those who were exposed to warfarin. Conversely, two other studies suggested no significant increase in the bleeding risk, in dialysis patients with or without dialysis exposure.

As proposed by Thet et al., HEMORR2HAGES [Hepatic or renal disease, Ethanol abuse, Malignancy history, Older

(age >75), Reduced platelet count or function, Rebleeding risk, History of past bleeding, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke history] and HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios, Elderly, Drugs or alcohol) are two bleeding risk assessment tools, which can be used in clinical practice in patients with atrial fibrillation to determine bleeding risk whilst on dialysis.

Antiplatelets Agents^{35,36}

A large population above the age of 50 years is on antiplatelet agents for some reason or the other. The DOPPS showed a varied incidence (3–25%) of the use of antiplatelet therapy amongst different countries. A study conducted in diabetic patients with an exposure to antiplatelets agents, confirmed substantially higher bleeding rates in the dialyzed versus nondialyzed groups. This risk further increased in patients receiving dual antiplatelet therapy. Though antiplatelet agents may have a small role in maintaining graft function of arteriovenous fistulas, adding an antiplatelet agent in dialyzed patients unless otherwise indicated, seems unnecessary.

Patients with Heparin Induced Thrombocytopenia³⁷⁻³⁹

Heparin induced thrombocytopenia is of two types. It is the type II, with platelet counts less than 30,000, which is of

clinical significance. The incidence of HIT is reported to be less than 1% for LMWH as compared to 3–5% due to UFH. The prevalence of HIT varies from 0 to 12% in dialysis patients. Heparin induced thrombocytopenia patients needing hemodialysis is a complex situation and can be tackled in the following three ways:

1. The immediate discontinuation of all heparin exposure on early suspicion of HIT
2. Use of alternative systemic anticoagulants
3. Transition to an anticoagulant.

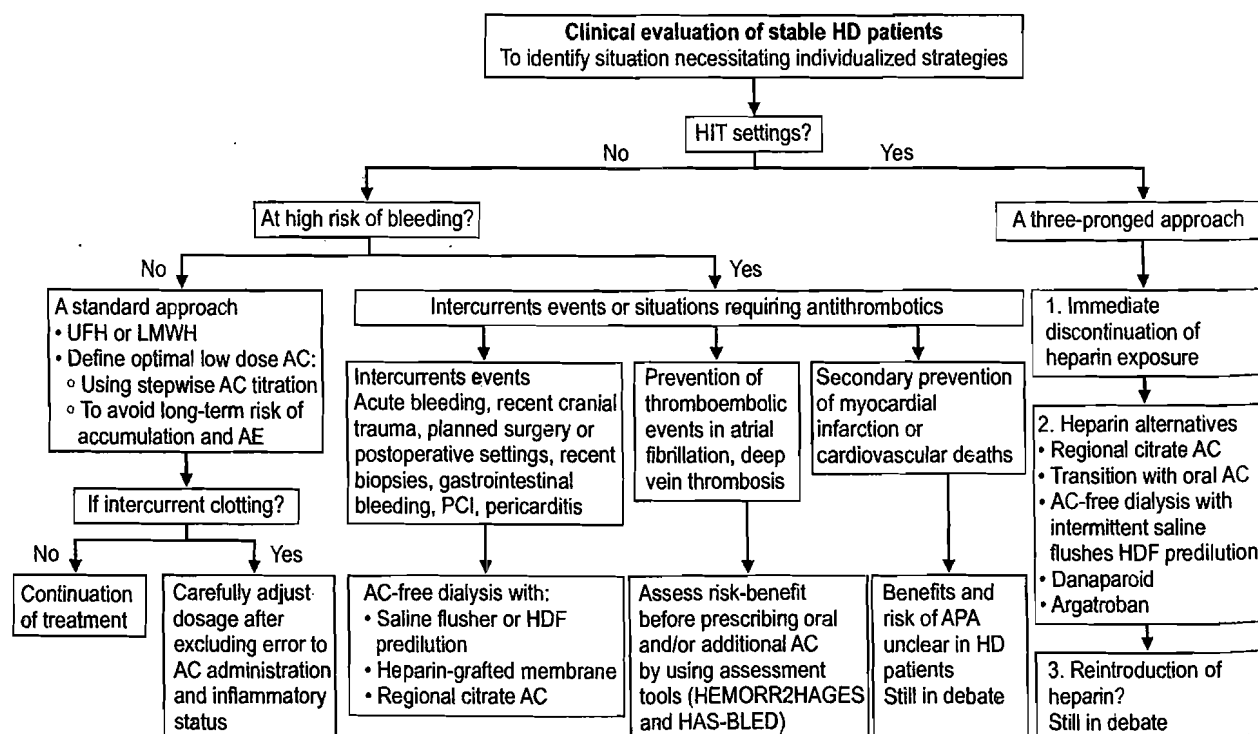
Tailoring of Anticoagulant Therapy

Optimization of anticoagulant therapy of individual dialysis patient necessitates a standardized protocol depending upon the patient profile as shown in flowchart 1.

Low heparin doses are safe and yet prevent clotting, however, a stepwise titration and or an anti-Xa measurement are recommended.

CONCLUSION

Anticoagulation in hemodialysis patients is beset with heterogeneity and lack of evidence based practice. Thus, most dialysis centers have adopted local strategies and protocols to avoid bleeding and clotting at both ends of the spectrum. A visual inspection and monitoring the compression time at needle puncture are age-old techniques still practiced by some dialysis units.



APA, antiplatelet agents; AC, anticoagulant; AE, adverse events; HD, hemodialysis; HIT, heparin induced thrombocytopenia; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; HDF, hemodiafiltration; HEMORR2HAGES, Hepatic or renal disease, Ethanol abuse, Malignancy history, Older (age >75), Reduced platelet count or function, Rebleeding risk, History of past bleeding, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke history; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios, Elderly, Drugs or alcohol.

FLOWCHART 1: Optimal approach to deliver systemic anticoagulation therapy in stable hemodialysis patients

A patient at low risk of bleeding could suddenly transform into a high risk group. These changing dynamics, mandate vigilance whilst using anticoagulants. In such settings, one may consider other alternative nonanticoagulant strategies.

It is a matter of philosophy whether a patient on dialysis should die of a life-threatening bleed or a major thromboembolic event. Thus, we need newer standardized and replicable bleeding risk assessment tools for these patients. The need of the hour is to develop newer and safer anticoagulants, which can also be monitored effectively. Research on the hemostasis phenotype could pave the path for the future.

REFERENCES

- Fischer KG. Essentials of anticoagulation in hemodialysis. *Hemodial Int*. 2007;11(2):178-89.
- Suranyi M, Chow JS. Review: anticoagulation for hemodialysis. *Nephrology*. 2010;15(4):386-92.
- Kerr P, Perkovic V, Petrie J, Agar J, Disney A. Caring for Australians with Renal Impairment (CARI): Dialysis adequacy (HD) guidelines. *Nephrology*. 2005;10(4):S61-80.
- European Best Practice Guidelines Expert Group on Hemodialysis: European Renal Association: Section V: chronic intermittent hemodialysis and prevention of clotting in the extracorporeal system. *Nephrol Dial Transplant*. 2002;17(7):63-71.
- Zoccali C, Abramowicz D, Cannata-Andia JB, Cochat P, Covic A, Eckardt KU, et al. European best practice quo vadis? From European Best Practice Guidelines (EBPG) to European Renal Best Practice (ERBP). *Nephrol Dial Transplant*. 2008;23(7):2162-6.
- Vanbelleghem H, Vanholder R, Levin NW, et al. The kidney disease: improving global outcomes website: comparison of guidelines as a tool for harmonization. *Kidney Int*. 2007;71(10):1054-61.
- Mactier R, Hoenich N, Breen C. Renal Association Clinical Practice Guideline on Haemodialysis. *Nephron Clin Pract*. 2011;118(1):c241-86.
- K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005;45(4):S1-153.
- Hirakata H, Nitta K, Inaba M, et al. Japanese Society for Dialysis Therapy Guidelines for management of cardiovascular diseases in patients on chronic hemodialysis. *Ther Apher Dial*. 2012;16(5):387-435.
- Pilmore H, Dogra G, Roberts M, Lambers Heerspink HJ, Ninomiya T, Huxley R, et al. KHA-CARI guideline: cardiovascular disease in patients with chronic kidney disease. *Nephrology*. 2014;19:3-10.
- Buturovic-Ponikvar J, Gubensek J, Ponikvar R: Regional citrate anti-coagulation for hemodialysis: calcium-free vs. calcium containing dialysate—a randomized trial. *Int J Artif Organs*. 2008;31(5):418-24.
- Szamosfalvi B, Frinak S, Yee J. Automated regional citrate anticoagulation: technological barriers and possible solutions. *Blood Purif*. 2010;29(2):204-9.
- Strobl K, Hartmann J, Wallner M, Brandl M, Falkenhagen D. A target-oriented algorithm for citrate-calcium anticoagulation in clinical practice. *Blood Purif*. 2013;36(2):136-45.
- Zimbudzi E. Intermittent saline flushes or continuous saline infusion: what works better when heparin-free dialysis is recommended? *Int J Nephrol Renovasc Dis*. 2013;6:65-9.
- Laville M, Dorval M, Fort J, et al. A randomized controlled multicenter trial of a heparin-grafted poly-acrylonitrile membrane for no-heparin hemodialysis versus standard-of-care: results of the HepZero study. *Kidney Int*. 2014;86(6):1260-7.
- Stamatiadis DN, Helioti H, Mansour M, et al. Hemodialysis for patients bleeding or at risk for bleeding, can be simple, safe and efficient. *Clin Nephrol*. 2004;62(1):29-34.
- Lee KB, Kim B, Lee YH, Yoon SJ, et al. Hemodialysis using heparin-bound hemophan in patients at risk of bleeding. *Nephron Clin Pract*. 2004;97(1):c5-10.
- Kodras K, Benesch T, Neumann I, et al. Comparison of two dialysers (AN69ST vs. X100) for heparin-free dialysis in patients with oral anti-coagulation. *Blood Purif*. 2008;26(3):226-30.
- Brunet P, Frances J, Vacher-Coponat H, et al. Hemodialysis without heparin: a randomized, controlled, crossover study of two dialysis membranes (AN69ST and polysulfone F60). *Int J Artif Organs*. 2011;34(12):1165-71.
- Sagedal S, Witczak BJ, Osnes K, et al. A heparin-coated dialysis filter (AN69ST) does not reduce clotting during hemodialysis when compared to a conventional polysulfone filter (FX8). *Blood Purif*. 2011;32(3):151-5.
- Ho G, Leblanc K, Selby R, Richardson R, Hladunewich M, Battistella M. Use of fondaparinux for circuit patency in hemodialysis patients. *Am J Kidney Dis*. 2013;61:525-6.
- Ulbricht K, Bucha E, Pöschel KA, et al. The use of PEG-hirudin in chronic hemodialysis monitored by the Ecarin Clotting Time: influence on clotting of the extracorporeal system and hemostatic parameters. *Clin Nephrol*. 2006;65(3):180-90.
- Poschel K, Bucha E, Esslinger HJ, et al. Anticoagulant efficacy of PEG-hirudin in patients on maintenance hemodialysis. *Kidney Int*. 2004;65(2):666-74.
- Vitale C, Berutti S, Bagnis C, et al. Dermatan sulfate: an alternative to unfractionated heparin for anticoagulation in hemodialysis patients. *J Nephrol*. 2013;26(1):158-63.
- Yixiong Z, Jianping N, Yanchao L, et al. Low dose of argatroban saline flushes anticoagulation in hemodialysis patients with high risk of bleeding. *Clin Appl Thromb Hemost*. 2010;16(4):440-5.
- Tsai T, Maddox TM, Roe MT, et al. Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. *JAMA*. 2009;302(22):2458-64.
- Rodger M, Ramsay T, MacKinnon M, et al. Tinzaparin versus dalteparin for periprocedure prophylaxis of thromboembolic events in hemodialysis patients: a randomized trial. *Am J Kidney Dis*. 2012;60(3):427-34.
- Furkert JD, Zeier M, Schwenger V. Gastrointestinal hemorrhage in hemodialysis patients. *Z Gastroenterol*. 2008;46(11):1266-9.
- Kuo CC, Kuo HW, Lee IM, et al. The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: a population-based cohort study. *BMC Nephrol*. 2013;14:15.
- Thet Z, Vilayur E. Atrial fibrillation and warfarin use in hemodialysis patients: an individualized holistic approach is important in stroke prevention. *Nephrology*. 2013;18(5):331-9.
- Juma S, Thomson BK, Lok CE, et al. Warfarin use in hemodialysis patients in atrial fibrillation: decisions based on uncertainty. *BMC Nephrol*. 2013;14:174.
- Genovesi S, Rossi E, Pogliani D, et al. The nephrologist's anticoagulation treatment patterns/regimens in chronic hemodialysis patients with atrial fibrillation. *J Nephrol*. 2014;27(2):187-92.
- Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. *Kidney Int*. 2013;84(3):600-8.
- Krummel T, Scheidt E, Bomi-Duval C, et al. Haemodialysis in patients treated with oral anticoagulant: should we heparinize? *Nephrol Dial Transplant*. 2014;29(4):906-13.
- Palmer SC, DiMicco L, Razavian M, et al. Antiplatelet therapy to prevent hemodialysis vascular access failure: systematic review and meta-analysis. *Am J Kidney Dis*. 2013;61(1):112-22.
- Daimon S, Terai H. Influence of antiplatelet medications on bleeding events in hemodialysis patients. *Ther Apher Dial*. 2011;15(5):454-9.
- Girtovitis FI, Boutou AK, Ioannidis G, et al. Heparin-induced thrombocytopenia type II. A treatment review. *Haema*. 2005;8(4):582-9.
- Davenport A. HIT on dialysis. When is it safe to re-challenge? *Nephron Clin Pract*. 2006;104(4):c149-50.
- Cuker A. Heparin-induced thrombocytopenia: present and future. *J Thromb Thrombolysis*. 2011;31(3):353-66.

Furosemide Stress Test

Arghya Majumdar

INTRODUCTION

Furosemide [4-chloro-N-(2-furyl methyl)-5-sulfamyl-anthranilic acid] was described as a novel and potent diuretic, which was efficacious when given either orally or parenterally.

Stason et al. studied 39 patients and 7 normal volunteers in 1966. The patients had congestive heart failure, cirrhosis of liver, nephritic syndrome, and malignant hypertension. All the patients demonstrated retention of renal sodium and water, and most were refractory to mercurials, acetazolamide, thiazides, and spironolactone administered singly or in combination. When administered furosemide, the natriuresis and diuresis were remarkable.¹

Over the years, furosemide has been utilized in the clinical setting of acute kidney injury (AKI) with varied intentions and purposes.

PHARMACOLOGY OF FUROSEMIDE

Furosemide, a weak organic acid, is mainly excreted by the kidneys (85%). Half of it is metabolized, and half is secreted actively in the proximal tubule by the organic acid transporters.² It is highly protein bound (>98%) and, therefore, a very small fraction of the drug can be filtered through the glomerulus.³ The binding of furosemide to plasma proteins enables its active renal secretion through the human organic anion transporter system in the proximal convoluted tubule and facilitates its diuretic effect.⁴ A decrease in the protein bound fraction of furosemide in hypoalbuminemia states or in the presence of another highly protein bound drug (e.g., warfarin, phenytoin) diminishes the tubular secretion of furosemide and its diuretic potency.⁴

Furosemide acts on the luminal sodium-chloride-potassium [Na-K-Cl₂] cotransporter of the ascending limb of the loop of Henle. It has also been seen to block the tubuloglomerular feedback response.⁵ It was conventionally used to potentiate renal excretion of excess salt and

water. Blocking the energy driven Na-K-Cl₂ transporters by furosemide helps to decrease cellular transport and diminishes energy consumption and hence increasing the chances of maintaining cellular viability. This mechanism of action of furosemide may have a protective action in AKI.⁶ The diuretic response to furosemide depends on the urinary concentration, the time of delivery to the site of action, and the dynamics of the response at the site of action.³

POTENTIAL ROLE OF FUROSEMIDE IN PROGNOSTICATING ACUTE KIDNEY INJURY

Acute kidney injury is associated with heightened risk of morbidity and mortality in critically ill patients and is the most common reason for nephrology consultation in inpatients.⁷⁻⁹ Despite an exponential rise in the incidence of AKI in recent years, physicians still lack the clinical tools to predict the likelihood of progression of AKI (defined as a worsening of AKI stage, such as advancing from stage 1 to 2 or 3) at an early stage.¹⁰

The pharmacology of furosemide suggests that the diuretic efficacy of furosemide is dependent on renal blood flow and the function of the proximal tubule and loop of Henle. Clinical studies suggest that nonoliguric AKI is a milder form of AKI than oliguric AKI^{11,12} and a good and sustained urinary output response to furosemide in the early stage of AKI may be considered to reflect a mild AKI, which has a lower chance of requiring dialysis.^{13,14} It is, however, the severity of AKI that determines whether a patient will respond to furosemide and not furosemide that portends the severity of AKI.

In patients who have developed AKI, a diminished diuretic response to furosemide may be due to a conglomeration of different mechanisms, which include decreased tubular secretion of furosemide and a suboptimal response of the Na-K-Cl₂ cotransporters at the loop of Henle.¹⁵ The diuretic response to furosemide seems to have a significant inverse correlation to the severity of AKI.¹⁴

OUTCOME OF USING FUROSEMIDE IN PREVENTION AND MANAGEMENT OF ACUTE KIDNEY INJURY

Bagshaw et al. published a systemic review and meta-analysis¹⁶ of the use of loop diuretics in acute renal failure in 2007, evaluating 65 studies, of which 5 were randomized controlled trials. The studies included 555 patients who were assessed and analyzed. The quality of these trials was deemed to be low. Comparing loop diuretics with control, there was no statistical difference in mortality [odds ratio (OR) 1.28; 95% confidence interval (CI), 0.89–1.84; $p = 0.18$] or renal recovery (OR 0.88; 95% CI 0.59–1.31; $p = 0.5$). Loop diuretics were, however, associated with a shorter duration of renal replacement therapy, shorter time to spontaneous decline in serum creatinine level and a greater increase in urine output from baseline. There was insufficient data regarding acid-base status, hospital length of stay, or health costs. The most common toxicity reported in 4 studies was transient tinnitus and deafness. However, these findings have limited relevance to critically ill patients as only 2 of the trials recruited critically ill patients.

Mehta and the Program to Improve Care in Acute Renal Disease (PICARD) study group did a cohort study,¹⁷ from 1989 to 1995, in the intensive care units at 4 medical centers. They recruited 552 patients with acute renal failure. Diuretics were prescribed in 326 patients (59%) at the time of nephrology consultation. Patients who had been treated with diuretics on or before the day of consultation were noted to be older and were more likely to have a background of congestive heart failure, nephrotoxic (rather than ischemic or multifactorial) etiology of acute renal failure, acute respiratory failure, and lower blood urea nitrogen concentrations. After adjusting for relevant covariates and propensity scores, use of diuretics was associated with a significant escalation in the risk of death or nonrecovery of renal function (OR 1.77; 95% CI 1.14–2.76). The risk was more pronounced (OR 3.12; 95% CI 1.73–5.62) when patients who died within the first week following consultation were excluded. Increased risk was seen mainly in patients who were relatively unresponsive to effect of diuretics.

Uchino and the Beginning and Ending Supportive Therapy for the Kidney (BEST kidney) investigators coordinated a prospective, multicenter, multinational epidemiologic study¹⁸ involving intensive care units from 54 centers in 23 countries. They recruited 1,743 patients who were either treated with renal replacement therapy (RRT) or fulfilled predefined criteria for acute renal failure. Three multivariate models were developed to analyze the relationship between use of diuretic and subsequent mortality. About 70% of patients were treated with diuretics at the time of inclusion. The most common conditions associated with occurrence of acute renal failure were severe sepsis/septic shock (43.8%), major surgery (39.1%), low cardiac output (29.7%), and hypovolemia

(28.2%). Furosemide was the most commonly used diuretic (98.3%). Combination therapy was given to 98 patients. In all 3 models, use of diuretics was not associated with a significantly increased risk of mortality, length of hospital stay, or dialysis dependence at the time of discharge.

Ho carried out a meta-analysis,¹⁹ evaluating 9 randomized controlled trials which included 849 patients. The outcome measures which did not significantly vary after furosemide treatment included inhospital mortality, necessity for requiring renal replacement therapy, number of sessions of dialysis required, and proportion of patients who continued to have persistent oliguria. Analyzing studies that used furosemide for prevention or treatment of acute renal failure did not alter the results regarding mortality and the necessity of requiring dialysis. The studies, however, indicated a heightened risk of tinnitus and temporary deafness in patients receiving high doses of furosemide.

FUROSEMIDE STRESS TEST

Need for a Prognosticating Test

Many patients who get AKI need RRT, but there is no consensus among nephrologists regarding the optimal time of commencing RRT. This decision-making becomes more arduous as patients with AKI are managed not just by nephrologists but by various other specialists—emergency medicine physicians, internists, intensivists, pediatricians, surgeons, and anesthesiologists. On the other hand, RRT is an invasive process with its associated risks, and one would not want to start this therapy if the patient were likely to recover kidney function with noninvasive management. However, an overcautious approach of starting RRT later in the course of AKI may lead to adverse results.²⁰ Thus, the need of a test that could predict the likelihood of advancing to a more severe stage of AKI, enabling timely, rational decisions regarding time of commencing RRT.

Rationale

The diagnosis of AKI by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria has some limitations. If decreasing urine output is considered as a criterion, nonoliguric AKI cannot be detected. On the other hand, creatinine has its inherent limitations. It is dependent on protein intake and muscle mass, it starts to increase quite late after AKI and the initial rise may be blunted by dilution ensuing from fluid resuscitation. This clinical need has led to research on multiple potential biomarkers of AKI, which increase early after tubular injury and have less confounding factors.²¹ However, AKI biomarker levels tend to vary over time according to the timing and severity of injury.²² Therefore, a functional assessment of the performance of the kidney might be synergistic to information provided by biomarker levels. As the most common type of intrinsic AKI

involves acute tubular necrosis, it would be logical to design a test for tubular function for this purpose.

Furosemide has pharmacokinetic properties, as a loop diuretic, that make it an appealing candidate molecule. In contrast to most other drugs eliminated by the kidney, furosemide is minimally filtered by the glomerulus but secreted by an active process in the proximal convoluted tubule. Thereafter, furosemide inhibits active chloride transport throughout the lumen of the thick ascending limb of the loop of Henle, thereby deterring sodium reabsorption and leading to natriuresis and enhanced urine flow.²³

Chawla et al. theorized that a furosemide stress test (FST) i.e., assessing the increase in urine output after a bolus of furosemide, might help to assess the integrity of renal tubular function at an early stage of evolving AKI. They postulated that the kidney's response or lack of response to a furosemide challenge would enable a clinical evaluation of renal tubular function and reserve. The availability of furosemide at the site of tubular action necessitates adequate renal blood flow and organic anion secretion in the proximal tubule, and the successful diuretic response requires no limitation to urine flow by intratubular obstruction by cellular debris. This could stratify patients with severe tubular injury before it is clinically obvious (by the RIFLE criteria). They aimed to develop and standardize a FST for patients with evolving AKI and describe its performance in a clinical setting.²⁴

The Test

Critically ill patients with incipient AKI, in Acute Kidney Injury Network (AKIN) stage I or II, who were loop diuretic naïve, were administered a standard dose of intravenous furosemide at the rate of 1 mg/kg. Those who had received furosemide in the previous 7 days, were likely to have a blunted response to furosemide and were, therefore, given furosemide at the rate of 1.5 mg/kg. The hourly urine output was measured thereafter for 6 hours and the total in the next 24 hours. The clinical outcome was noted. To obviate the risk of hypovolemia, urine output was replaced mL for mL each hour, with either normal saline or Ringer's lactate for 6 hours after the FST, except in a situation where the volume loss was clinically desirable.²⁴

Study Methodology

Two cohorts of patients were studied.

Cohort 1

The first cohort was the Southern Acute Kidney Injury Network (SAKInet), which was formed in 2007 to collect samples from patients who developed AKI, with the aim of testing the diagnostic and prognostic accuracy of previously described and novel AKI biomarkers.²⁴

Cohort 2

Urine sediment was analyzed with the George Washington Urine Sediment Score (GW USS). Patients with a GW USS more than 2 with evidence of granular or epithelial cell casts in the urine sediment.²⁴

Study Criteria

Inclusion criteria:

- Age >18 years, admitted in ICU
- Acute Kidney Injury Network stage I [6 h of oliguria (<0.5 mL/kg/h) and/or 0.3 mg/dL increase in serum creatinine or increase of 150–200% above baseline serum creatinine], or AKIN stage II [12 h of oliguria (<0.5 mL/kg/h) and/or increase of 200–300% above baseline serum creatinine]
- Indwelling urinary catheter
- Presence of granular or epithelial cell casts in the urine sediment (defined by GW USS ≥ 2), or fractional excretion of sodium (FeNa) >1.0%, and
- Patient considered by the treating clinical team to be well-resuscitated.²⁴

Exclusion criteria:

- Baseline estimated glomerular filtration rate below 30 mL/min/1.73 m²
- Renal allograft
- Known pregnancy
- Evidence of obstructive uropathy (e.g., hydroureteronephrosis)
- Presence of active bleeding
- Patients with documented allergy or sensitivity to loop diuretics
- Achievement of AKIN stage III criteria, or
- Evidence of central volume depletion at the time of furosemide administration.²⁴

Outcome Targets

The primary outcome noted was the progression to AKIN stage III (need for RRT, increase in serum creatinine of 300% over baseline, urine output of 0.3 mL/kg/h \times 24 h) within 2 weeks of FST.²⁴

The secondary outcome noted was the aggregate of developing AKI, stage AKIN III, or death within 2 weeks of the FST.²⁴

Results

A total of 77 patients were studied, 23 patients from cohort 1 and 54 patients from cohort 2. Of the total 77 patients, 25 (32.4%) met the primary outcome of AKI, AKIN stage III, and 16 (20.7%) died. Of the total patients, 32 (41.5%) met the secondary composite endpoint of AKI, AKIN III, or death

within 14 days of the FST. Of the 25 patients who advanced to AKI, AKIN stage III, RRT was needed in 11 (44.0%).²⁴

In total, 24 patients (31%) had underlying chronic kidney disease (CKD). The progressors and nonprogressors were well-matched with regard to comorbidities like diabetes, hypertension, congestive heart failure, or CKD; nephrotoxic exposure; sepsis, cardiothoracic surgery; serum albumin, lactate, or severity of disease as measured by Acute Physiology and Chronic Health Evaluation (APACHE) II or the Cardiovascular Components-Sequential Organ Failure Assessment (CV-SOFA) scores.²⁴

The baseline urinary flow rate (UFR) noted for 6 hours before the FST was 74.2 (11.6) mL/h. The baseline UFR seen was 95.7 (16.3) and 29.7 (4.2) in the nonprogressor group compared to the progressor group ($p < 0.01$). They analyzed the ability of the UFR in absolute values (UFR-raw), the UFR that was corrected for ideal body weight (UFR-IBW), and the UFR that was corrected for actual body weight (UFR-ABW) to predict progression to AKI, AKIN stage III. The receiver operating characteristic-area under curve (AUC) calculated for UFR-raw, UFR-IBW, and UFR-ABW was 0.76 (0.09), 0.71 (0.08), and 0.76 (0.08), respectively.²⁴

There were lesser number of patients with AKIN stage II in the nonprogressors [$n = 18$ (34.6%)] group compared to progressors [$n = 18$ (72%)] ($p < 0.003$).²⁴

Specifics of the Furosemide Stress Test

The urine output after FST (for each increase of 10 mL of urine output) was predictive of nonprogression to AKI, AKIN stage III, when baseline patient imbalances were placed into a multivariate logistic regression analysis (OR 0.98, 95% CI 0.96–0.99, $p = 0.05$).

The FST was well-tolerated with no documented episodes of hypotension or any other significant adverse event considered attributable to the test. Furosemide administration can cause vasodilation and hypotension, but these were not observed during the study. Adequate steps were taken to diminish the chance of this potential adverse effect by ensuring that the patients were considered clinically well-resuscitated before commencing the test and when appropriate, the volume of urine output was replaced with isotonic fluids. This may explain to a large extent why no adverse events were observed. The maximum UFR was seen within the first 2–3 hours.²⁴

The UFR in response to the FST was compared between those subjects that progressed and those that did not progress to AKI, AKIN stage III. For each hourly interval, progressors had a lower UFR response when compared to nonprogressors ($p < 0.001$). The UFR of FST between patients who were furosemide naïve were compared to those that were not and no difference was noted between these. Various combinations of the urine output intervals were analyzed, to assess which one had the best discriminating capacity. It was deduced that the sum of the first 2 hours of urine output after FST had the highest AUC to predict the primary outcome

(0.87 in both cohorts 1 and 2). The 2-hour urine output of 200 mL or less had the highest sensitivity and specificity to predict the primary outcome.²⁴

These findings support the conjecture that the FST offers important clinical information not apparent from the baseline UFR alone.²⁴

Critique

Though the findings from Chawla's study²⁴ make the point that FST has good prognosticating ability, one has to remember that using it in a patient who has not been appropriately fluid resuscitated may be counterproductive. It is crucial for the patient to be euvolemic before venturing into any sort of furosemide challenge. It is also vital to replace volume in patients who are not clearly volume overloaded, as the mean urine output seen in response to the FST was >1.3 L in 6 hours. Moreover, the FST can be carried out only in a clinical setting where the heart rate, blood pressure, and urine output can be monitored closely.²⁴

Though previous studies in AKI have failed to clearly demonstrate a beneficial clinical effect, theoretically, furosemide has the potential for saving energy and oxygen consumption, and protecting the tubules, during an ischemic insult. Therefore, one cannot be certain that furosemide administration did not affect the natural history of progression of AKI and, therefore, could not have affected its prognostic ability.¹⁷ In addition, the study did not include patients with nephritic syndrome, acute decompensated heart failure, cirrhosis of liver, or other subjects with resistance to diuretics. Therefore, one cannot presume that the FST will perform in the same way in these patient populations.²⁴

FUROSEMIDE STRESS TEST COMPARED TO ACUTE KIDNEY INJURY BIOMARKERS

In patients with early AKI (stage I), a number of biomarkers of AKI, including plasma or urinary neutrophil gelatinase associated lipocalin (NGAL), urinary interleukin (IL)-18, kidney injury molecule (KIM)-1, tissue inhibitor of metalloproteinases (TIMP)-2, and insulin-like growth factor binding protein-7 (IGFBP-7) have shown variable potential to predict progression of AKI.^{21,22,25,26} However, despite a plethora of studies, the utility of these and other evolving biomarkers remain uncertain. Moreover, most intensivists and nephrologists do not have clinical access to these biomarker assays, which are still mainly in the realm of research.

Subsequent to their previous study, Koyner et al. compared the performance of several AKI biomarkers—FeNa, urine albumin-to-creatinine ratio, urine and plasma NGAL, KIM-1, urinary IL-18, TIMP-2, IGFBP-7, and uromodulin with the performance of FST for the ability to predict progression of AKI, necessity for RRT, and mortality.²⁷

Urine output in the first 2 hours after FST outperformed most of the biomarkers of AKI when predicting progression

of AKI and future necessity of RRT. Furosemide stress test, in particular, was better than the complete panel of biomarkers at predicting advancement to AKIN stage III. The complementary addition of biomarkers to results of FST did not provide any additional benefit. Moreover, FST was better than all other biomarkers in predicting the combined endpoint of RRT requirement and death.²⁷

Further, when prespecified biomarker cutoffs were used, the performance of FST to predict patient outcomes in this "high-risk" subset, was increased, when compared with FST alone. Forty four (57.1%) patients had a urine NGAL concentration >150 ng/mL before FST. In this subgroup, FST could portend the development of all four outcomes (progression to stage III, receipt of RRT, death, and the composite endpoint). The AUC for the prediction of need for RRT was 0.91 ± 0.06 ($p < 0.001$), while the AUC for the composite endpoint of stage III AKI or death was 0.89 ± 0.06 ($p < 0.001$).²⁷

FUTURE POTENTIAL OF FUROSEMIDE STRESS TEST

Nephrologists can take a leaf out of cardiology practice and use the concept in managing patients with AKI. Patients developing renal angina²⁸ can undergo evaluation with AKI biomarkers in the initial stage. Patients in whom AKI is established with the levels of biomarkers, maybe then subjected to a FST, an assessment of renal reserve and of integrated renal function—renal blood flow, organic acid secretion, thick ascending function, and tubule luminal patency, to get an idea about the severity, risk of progression, and prognosis of AKI.²⁹ Of course, one should keep in mind the fact, that use of loop diuretics without a protocol and close monitoring can be detrimental. Furosemide stress test should be conducted only after adequate fluid resuscitation, preferably as an inpatient in a facility where proper monitoring is ensured. The FST should not be utilized as a primary screening procedure to diagnose AKI.²⁷

Improving risk prediction ability in patients with early AKI can alter clinical decision-making and patient care, besides facilitating recruitment into further AKI trials. Future studies are mandated to fully explore the potential and appropriate utilization of FST along with biomarkers in this regard.

CONCLUSION

The furosemide stress test provides a tool for assessing the integrity of renal tubular function at an early stage of evolving AKI. The kidney's response or lack of response to a furosemide challenge facilitates a clinical evaluation of renal tubular function and reserve.

Improving risk prediction ability in patients with early AKI can alter clinical decision making and patient care, besides enabling recruitment into further AKI trials. Future studies are mandated to fully explore the potential and appropriate utilisation of FST along with biomarkers in this regard.

REFERENCES

1. Stason WB, Cannon PJ, Heinemann HO, et al. Furosemide: A clinical evaluation of its diuretic action. *Circulation*. 1966;34:910-20.
2. Pichette V, du Souich P. Role of the kidneys in the metabolism of furosemide: its inhibition by probenecid. *J Am Soc Nephrol*. 1996;7:345-9.
3. Brater DC. Resistance to diuretics: emphasis on a pharmacological perspective. *Drugs*. 1981;22:477-94.
4. Pichette V, Geadah D, du Souich P. Role of plasma protein binding on renal metabolism and dynamics of furosemide in the rabbit. *Drug Metab Dispos*. 1999;27:81-5.
5. Nishiyama A, Majid DS, Walker M III, et al. Renal interstitial ATP responses to changes in arterial pressure during alterations in tubuloglomerular feedback activity. *Hypertension*. 2001;37:753-9.
6. Brezis M, Rosen S, Silva P, et al. Transport activity modifies thick ascending limb damage in the isolated perfused kidney. *Kidney Int*. 1984;25:65-72.
7. Chertow GM, Levy EM, Hammermeister KE, et al. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med*. 1998;104:343-8.
8. Koyner JL, Cerdá J, Goldstein SL, et al.; Acute Kidney Injury Advisory Group of the American Society of Nephrology: The daily burden of acute kidney injury: A survey of US nephrologists on World Kidney Day. *Am J Kidney Dis*. 2014;64:394-401.
9. Ahmed US, Iqbal HI, Akbar SR. Furosemide in acute kidney injury—A vexed issue. *Austin J Nephrol Hypertens*. 2014;1(5):1025.
10. Hsu RK, McCulloch CE, Dudley RA, et al. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol*. 2013;24:37-42.
11. Frankel MC, Weinstein AM, Stenzel KH. Prognostic patterns in acute renal failure: the New York Hospital, 1981-1982. *Clin Exp Dial Apheresis*. 1983;7:145-67.
12. Bellomo R, Ronco C, Kellum JA, et al.; Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204-12.
13. Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, doubleblind, placebo-controlled, randomized study. *Nephrol Dial Transplant*. 1997;12(12):2592-6.
14. Ho KM, Walters S, Faulke D, et al. Clinical predictors of acute renal replacement therapy in critically ill patients with acute renal impairment. *Crit Care Resusc*. 2003;5:97-102.
15. Brater DC. Resistance to diuretics: emphasis on a pharmacological perspective. *Drugs*. 1981;22:477-94.
16. Bagshaw SM, Delaney A, Haase M, et al. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. *Crit Care Resusc*. 2007;9:60-8.
17. Mehta RL, Pascual MT, Soroko S, et al.; PICARD Study Group. Diuretics, mortality, and non-recovery of renal function in acute renal failure. *JAMA*. 2002;288:2547-53.
18. Uchino S, Doig GS, Bellomo R, et al. Beginning and Ending Supportive therapy for the Kidney (B.E.S.T. Kidney) Investigators. *Crit Care Med*. 2004;32:1669-77.
19. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ*. 2006;333(7565):420.
20. Seabra VF, Balk EM, Liangos O, et al. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. *Am J Kidney Dis*. 2008;52:272-84.
21. Bonventre JV. Diagnosis of acute kidney injury: from classic parameters to new biomarkers. *Contrib Nephrol*. 2007;156:213-9.
22. Devarajan P. Emerging biomarkers of acute kidney injury. *Contrib Nephrol*. 2007;156:203-12.
23. Burg M, Stoner L, Cardinal J, et al. Furosemide effect on isolated perfused tubules. *Am J Physiol*. 1973;225:119-24.
24. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care*. 2013;17:R20.
25. Koyner JL, Garg AX, Coca SG, et al; TRIBE-AKI Consortium. Biomarkers predict progression of acute kidney injury after cardiac surgery. *J Am Soc Nephrol*. 2012;23:905-14.
26. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.
27. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. *J Am Soc Nephrol*. 2015;26:1-27.
28. Goldstein SL, Chawla LS. Renal angina. *Clin J Am Soc Nephrol*. 2010;5:943-9.
29. Powell TC, Warnock DG. The furosemide stress test and predicting AKI outcomes. *J Am Soc Nephrol*. 2015;26:1-3.

Continuous Renal Replacement Therapy in India: Is It Cost-effective?

Yash Javeri, Deven Juneja

INTRODUCTION

The past couple of years have seen a dramatic change in critical care. Advanced technologies and monitoring techniques with standardized definitions have together increased the diagnostic and therapeutic capabilities of a critical care specialist. Such is also the case with acute kidney injury (AKI). The incidence of AKI has been increasing, especially in intensive care unit (ICU), and is a cause for concern as it is an independent predictor of mortality.^{1,2} This could be due to increasing prevalence of lifestyle diseases with already compromised but stable renal function, superimposed infections, as well as increased rates of detection. Acute kidney injury is not a disease per se, but represents a spectrum of disorders ranging from mild-to-severe loss of kidney function. As the name suggests, AKI is a sudden decline in the function of kidneys with retention of nitrogenous waste products or decline in urine output or both. Earlier definitions for AKI were inconsistent and changeable. As a result, epidemiological studies were unable to estimate the exact prevalence of AKI in hospitals and ICUs. Initial studies using different criteria estimated the prevalence of AKI in ICU ranging from 1 to 70%.³⁻⁵

Thus, the need of the hour was to frame a universally acceptable standard definition for diagnosis of AKI. The Acute Dialysis Quality Initiative developed the Risk, Injury, Failure, Loss of kidney function, End-stage renal disease (RIFLE) classification of AKI in 2004.⁶ The RIFLE criteria is based on changes in serum creatinine levels, glomerular filtration rate, and decline in urine output from baseline. Using these variables, it helps identify kidneys at risk of damage, already compromised kidneys, and finally established renal failure. As a result, it aids in management decisions.

INCIDENCE OF ACUTE KIDNEY INJURY IN INTENSIVE CARE UNITS AND HOSPITALS

The incidence of AKI is said to range from 5 to 7% in hospitalized patients and is on an upward trend.⁷⁻¹⁰

However, there is still scarcity of data regarding the prevalence of AKI in ICUs. A few studies have shown that the overall incidence of AKI in ICU is around 20–50%.¹¹⁻¹⁴ The exact burden of chronic kidney disease (CKD) in India still remains undefined with only limited data from the 3 population-based studies addressing this issue.¹⁵⁻¹⁷ The Chronic Kidney Disease Registry, recently established by the Indian Society of Nephrology, may provide useful epidemiological data in the future. In the prevention study done in Chennai, the prevalence at the community level is 8,600 per million population (pmp) in the study group and 13,900 pmp in the control group.¹⁵ A study based in Delhi revealed a prevalence of CKD (serum creatinine >1.8 mg/dL) at 7,852 pmp.¹⁶ Another study from Bhopal revealed an incidence of 151 pmp suffering from end-stage renal disease (ESRD).¹⁷ Do we have the resources and skill to handle this ever increasing population of ESRD in India?

Acute kidney injury in ICU occurs secondary to multiple causes, the most common being prerenal AKI. Prerenal AKI is secondary to a systemic cause, which if timely corrected, would return the kidney function back to normal within a short period of time.

The primary aim of AKI management is to prevent progression to acute tubular necrosis (ATN) as 20% cases of ATN progress to CKD within 1.5–2 years.¹⁸ Acute kidney injury itself is associated with longer length of hospital stay, progression to CKD or ESRD, and the most dreaded complication increased mortality. These patients are also more prone to develop other nonrenal comorbidities, which together with AKI, are associated with higher mortality.¹⁹⁻²² Even uncomplicated AKI is associated with longer hospital stays and higher resource utilization, further escalating the cost of therapy.²² Thus, early recognition of this condition is associated with the best possible outcome, both short term (clinically and economically) and long term.

In spite of early detection and correct management of AKI, a significant proportion of AKI patients do deteriorate to eventually develop CKD or ESRD. The exact mechanisms for this are unknown, but patients with preexisting CKD or

compromised kidney function were more prone to develop ESRD. Prescott et al. showed that about 53% of patients with CKD developed ESRD with AKI as compared to 13% cases without any preexisting renal dysfunction.²³ A multinational, multicenter study by Uchino et al. showed that 5.7% of cases with AKI eventually needed dialysis and these patients had a high mortality rates of >60%.³ Hoste et al. showed that around 0.2–0.3% of patients who developed AKI per year eventually required renal replacement therapy (RRT), and despite therapy, had a high mortality.²⁴ Results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) trial showed that 13% of patients with AKI required RRT on hospital discharge.³ Other factors which have been shown to be associated with poor outcomes are advanced age, diabetes mellitus, hypoalbuminemia, and severity of AKI.²⁵ High RIFLE class on admission or an increasing trend during hospital stay is associated with increasing mortality.^{26,27} Despite high prevalence of terminal events in patients of AKI, use of RRT in AKI have shown improved mortality rates.^{28,29}

WHAT IS RENAL REPLACEMENT THERAPY?

Renal replacement therapy is a form of artificial therapy to take over the functions of the kidneys in an effort to provide the damaged kidneys rest and time for recovery. It comprises of dialysis, hemofiltration, and hemodiafiltration.

PRINCIPLES OF DIALYSIS

Dialysis therapies involve removal of fluid and solutes by two processes, i.e., diffusion or convection used either alone or in combination. A hemofilter/hemodialyzer is used for the same wherein a semipermeable membrane separates the blood compartment from the dialysate compartment.

Diffusion is the process of movement of solute along a concentration gradient. Hemodialysis is primarily diffusion occurring across a semipermeable membrane. Blood flows over a semipermeable membrane separating it from dialysate which is flowing in the opposite direction. Small molecules with greater velocity are more freely cleared as compared to larger molecules. Inversely water moves freely from an area of high osmolality to low osmolality. With large shifts of water across the membrane, some solute molecules may be pulled along with it, a phenomenon called solvent drag.

Convection is the process of solute clearance across a semipermeable membrane by hydrostatic pressure gradient. All solutes with size smaller than the membrane pore size are removed in a proportion equivalent to their plasma concentration. Thus, this method of fluid removal is termed hemofiltration or ultrafiltration.

VARIOUS MODALITIES

The various dialysis techniques used in the ICU are hemodialysis, continuous renal replacement therapies (CRRTs), and peritoneal dialysis.

Continuous Renal Replacement Therapy

Continuous renal replacement therapy comprises of various dialytic modalities which differ in their mode of solute and water removal and duration of treatment. However, all are characterized by slow solute and fluid removal over a prolonged period of time. Solute removal is achieved by convection, diffusion, or a combination of both techniques.

Types

The various types of CRRT include:

- Continuous arteriovenous hemofiltration, hemodialysis, and hemodiafiltration
- Continuous venovenous hemofiltration, hemodialysis, and hemodiafiltration
- Slow continuous ultrafiltration.

Continuous Arteriovenous Systems

At the beginning of CRRT, arteriovenous systems were used which used to function on the pressure gradient between arterial and venous circulation for ultrafiltration to occur. However, since ICU patients were hemodynamically unstable with fluctuating arterial pressures, there was erratic and unreliable solute and fluid clearance. Also, this system required the long-term care of femoral arterial catheters. With the advent of advanced venovenous systems, arteriovenous systems have been gradually abandoned.

Continuous Venovenous Systems

They are of three types, viz., continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration.

Continuous Venovenous Hemofiltration

It is a convective process where a pump drives blood through a hemofilter and hydrostatic pressures play a role in the generation of ultrafiltrate. Large volumes of water and essential solute lost in the filtrate need to be replaced. Replacement fluid not containing targeted solutes for removal is administered either before (predilution) or after the filter (postdilution).

Continuous Venovenous Hemodialysis

It is a diffusive process wherein two pumps are used which drive blood and dialysate through a hemofilter in opposite

directions. The blood flow rate is much higher than the dialysate flow rate in this countercurrent system. This helps achieve complete balance in solute concentration across the membrane. The amount of ultrafiltrate produced is lesser than CVVH as the pressure gradient across the membrane is reduced with infusion of dialysate.

Continuous Venovenous Hemodiafiltration

This modality combines diffusion and convection together into a single procedure. It uses high rates of ultrafiltration combined with countercurrent dialysate flow to enhance solute clearance.

Slow Continuous Ultrafiltration

As the name suggests, it is a slow continuous ultrafiltration, wherein a pump maintains blood flow at <100 mL/min through a hemofilter. Ultrafiltration occurs at a slow rate of around 100–300 mL/h. This modality has negligible effect on the biochemical profile of the patient as it primarily removes water which is in proportion to solute. Hence, it is commonly used in volume overloaded patients with an acceptable biochemistry profile.

The differences between the various types of CRRT are shown in the table 1.

Indications

The indications of CRRT are the same as those for intermittent hemodialysis (IHD) or slow low efficiency dialysis. They include:

- Volume overload refractory to diuretic therapy. It is seen in around 30–70% cases of AKI in ICU. It is associated with increased risk of mortality and morbidity³⁰
- Uremia: Overt uremic signs and symptoms like uremic pericarditis, encephalopathy, or uremic bleeding diathesis are absolute indications to initiate RRT
- Metabolic acidosis refractory to medical therapy: In renal failure, there is fixed acid production. Recalcitrant acidosis with a pH <7.15 is a common indication to initiate RRT

- Hyperkalemia not responding to medical therapy: No specific potassium level has been defined to initiate RRT in hyperkalemia. However, RRT is not initiated at serum potassium below 6.5 mmol/L
- Hypermagnesemia, hypercalcemia
- Severe hypo-/hypermnatremia
- Drug overdose/toxins: Overdose/intoxications with dialyzable drugs (salicylate, theophylline, lithium, methotrexate, methanol, and ethylene glycol) are relative indications for RRT
- Temperature control: Rarely, RRT is used in intractable hyperthermia as a method of cooling³¹
- Progressive azotemia.

Advantages and Disadvantages

Compare to IHD, CRRT offers several advantages which include that it is better tolerated by hemodynamically unstable patients as it causes less hypotension. As a result, it may support recuperation of kidneys from AKI. In addition, compared to IHD, it promotes greater solute clearance. Large volumes of fluid can be removed with CRRT. Continuous renal replacement therapy is also associated with lesser chances of dialysis disequilibrium syndrome as it does not cause drastic osmotic shifts. Some modalities, like CVVH, may remove harmful immunomodulatory substances in patients with sepsis.

However, it must be noted that CRRT also has certain disadvantages. Firstly, it needs continuous anticoagulation. Anticoagulation can be systemic or regional. Systemic anticoagulation with heparin can further complicate patient care with bleeding and heparin induced thrombocytopenia. Regional anticoagulation with citrate is considered safer as it does not increase the risk of bleeding. Continuous renal replacement therapy precludes patient mobilization and may increase the risk of pressure sores and difficult to transfer patients for investigations. The commonest metabolic abnormality associated with CRRT is hypophosphatemia. It is associated with loss of trace elements and may increase the risk of catheter related blood stream infection.

TABLE 1 Various types of continuous renal replacement therapy

Technique	Physical principle	Blood flow (mL/min)	Dialysate flow (mL/min)	Filtrate (L/day)	Renal flow (L/day)	Effluent saturation (%)	Duration (h)
Slow continuous ultrafiltration	Convection	<100	0	0–4	0	100	Variable
Continuous venovenous hemofiltration	Convection	200–400	0	48–96	46–94	100	24
Continuous venovenous hemodialysis	Diffusion + some convection	100–200	17–34	0	0	85–100	24
Continuous venovenous hemodiafiltration	Diffusion + convection	100–200	17–34	24–48	23–44	85–100	24

COST OF RENAL REPLACEMENT THERAPY

Every treatment modality comes with a price. Critically ill patients with AKI not only consume a major chunk of the dwindling resources but also increase healthcare costs. Since no specific modality is considered ideal, the type of RRT preferred differs amongst countries.³² A patient can be a suitable candidate for either modality.³³ Thus, cost may play a significant role when deciding which modality to choose. The cost of continuous and intermittent RRT differs and depends on various factors which can be broadly divided into two groups, i.e., direct costs and long-term costs. Direct cost may further be divided into cost of equipment, replacement fluids, anticoagulation, and nursing costs. Long-term costs include length of ICU stay, need for long-term dialysis, quality of life, and effect on mortality. Another facet to cost of therapy is related to adverse events arising during treatment. These events could range from fluid and electrolyte abnormalities to acid base disorders, medication overdoses, and dietary restrictions. Hence, it is essential to incorporate these factors while estimating the cost for managing AKI.

Direct Costs

Nursing Costs

On the face of it, it would seem that the nursing costs would be higher for patients on CRRT, as it is a more labor intensive therapy. However, nursing practices with respect to RRT differ amongst different countries and within regions of the same country which would impact the nursing costs. In many countries, intermittent renal replacement therapy (IRRT) is delivered by a hemodialysis nurse under the guidance and supervision of a nephrologist, while CRRT is delivered by ICU nurses under the guidance of a critical care specialist. The BEST Kidney investigators in their study in 2010 obtained and analyzed data from 44 centers across 23 countries. They concluded that nursing costs with IRRT was greater compared to CRRT in most centers, except Southern America where CRRT was costlier.³⁴ A possible explanation to this difference could be the extra cost incurred to train a dialysis nurse and the need for an extra staff to troubleshoot and manage the dialysis machine. Since CRRT is mainly administered by an ICU nurse who tends to the patient, it saves the cost of an extra staff which could be a substantial financial relief.³⁵ However, in India, both the forms of RRT are commonly administered by a dialysis nurse under the joint supervision of a nephrologist and intensivist. This is because of lack of training of ICU nurses to handle dialysis equipment. The training of ICU nurses could reduce the cost but would put additional responsibility on the staff.

Dialysate and Replacement Fluid Cost

Continuous renal replacement therapy is associated with higher fluid costs as compared to IRRT and is a major contributor to the overall cost difference between the two modalities. A part of this cost could be secondary to high volume CRRT (>25 mL/kg/h) performed at certain centers. The BEST investigators³⁴ estimated that decreasing the ultrafiltration flow rates to 25 mL/min would reduce fluid costs by approximately 43.3% and the overall cost of therapy by 19.5%. They further calculated that reducing the flow rate to <25 mL/kg/h would reduce total cost by a further 23.2%. The concern here is whether patient outcome is affected by reducing the flow rate. As per the Acute Renal Failure Trial Network (ATN) study and the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study, higher effluent flow rates of 35 and 40 mL/kg/h were not associated with any survival benefit.^{36,37} Hence, reducing the flow rate to 25 mL/kg/h could be an effective cost-saving strategy whenever there is a need for CRRT.

Anticoagulation

The extracorporeal circuit used during dialysis activates the coagulation system and hence, anticoagulation is needed to prevent clotting in the circuit. The type of anticoagulation used depends on the RRT modality and the patient profile. Usually, IRRT requires intermittent, while CRRT requires continuous anticoagulation. The most commonly used anticoagulant during dialysis is heparin (unfractionated or low molecular weight heparin). Sometimes, regional anticoagulation with citrate is used in cases of CRRT. Even though the dose of anticoagulant used in CRRT is higher due to its continuous administration, the BEST investigators³⁴ showed that the difference in cost for anticoagulation between CRRT and IRRT was not significant. One exception to this was Japan, where the anticoagulation cost for CRRT was much higher than for IRRT. This difference was because 50% of the patients received a serine protease inhibitor called nafamostat mesylate for anticoagulation.³⁸ Since this drug is much more expensive than unfractionated or low molecular weight heparin anticoagulation, it contributed significantly to increased cost of CRRT in Japan.

Extracorporeal Circuit Cost

The extracorporeal circuit comprises vascular access with indwelling venous catheter, blood lines, a pump driven blood circuit, and dialyzers. The cost and maintenance of a CRRT machine is much higher than the cost of a hemodialysis machine. A study by Mehta et al. showed that the material costs for CRRT were significantly higher than the costs for IHD. A major portion of this expense was attributed to the dialysate

used which attributed to about 33% of the total cost of CRRT.³⁹ An Italian study also showed that CRRT was 12% costlier than IHD with about 79% attributed to material cost.⁴⁰

Long-term Costs

Length of Intensive Care Unit Stay

It might be difficult to directly correlate the ICU length of stay with the type of RRT used. A trial by Rauf et al.⁴¹ showed that the mean adjusted length of ICU stay was 9.5 days shorter with IHD compared to CRRT. However, it should also be understood that CRRT is used in decompensated patients who are hemodynamically unstable and are on vasopressors with high ventilator requirements. So was the case in the study by Rauf et al. Patients with multiorgan failure will obviously have longer ICU stays compared to less critically ill patients.

Effect on Mortality

The debate over which modality is superior, CRRT or IRRT, is a never-ending topic. Some research shows that CRRT is better than IRRT.⁴²⁻⁴⁴ However, multiple studies have concluded that the type of modality used for managing patients with AKI, does not affect the overall mortality. A multicenter trial conducted by Vinsoneau et al., did not show a survival benefit at 60 days between the CRRT and IHD group.⁴⁵ Similar results were found by Pannu et al., with no difference in all-cause mortality in 7 randomized controlled trials (RCTs).⁴⁶ A meta-analysis of 9 RCTs showed no correlation between the type of RRT modality and mortality.^{46,47} Rauf et al. too concluded that the type of RRT method used did not show any difference in terms of renal recovery or mortality (both inhospital and postdischarge).⁴¹ Thus, which modality to choose would depend on patient characteristics, disease decompensation, and physicians' preference.

Need for Long-term Dialysis

Even though a large number of patients initiated on dialysis during acute therapy recover, a significant few do need dialysis at hospital discharge. Possible reasons could be the slow recovery of kidney function or in some cases, permanent loss of kidney function. As per the BEST Kidney trial, around 13% of patients with AKI needed dialysis at discharge.³

Similarly, other studies have also showed that about 10-30% of patients initiated on RRT in-hospital needed further dialysis treatment after discharge.^{48,49} Several factors have been identified which may increase the chances of requiring long-term dialysis, but the role of initial mode of RRT is still unclear. Previous literature suggested that the initial modality may not have an effect on renal recovery as an independent variable.⁴⁷ However, results from more recent trials suggest that long-term dialysis dependence may be lower in patients

who were initially managed by CRRT. A study by Olivier et al.⁵⁰ compared the use of initial CRRT and IRRT with long-term dialysis dependence and analyzed it from an economical perspective. They concluded that initial use of CRRT in AKI patients was cost-effective as compared to initial IRRT as it reduced the need for long-term dialysis. A recently published meta-analysis by Schneider et al. also showed that higher rates of dialysis dependence was seen when patients were initially managed with IRRT as compared to initial CRRT.⁵¹ Similarly, a retrospective study by Wald et al. also confirmed the above results with the need for chronic dialysis lower in patients who received CRRT as the initial RRT modality as compared to IRRT.⁵²

Quality of Life

An important aspect of any therapy is to achieve the best possible quality of life for the patient. Even if on long-term dialysis, the patient should not become a burden on his family. This may directly and indirectly increase the long-term costs associated with RRT. Multiple studies have been conducted on cost-effectiveness of RRT modality and its impact on the quality of life and most of them have suggested that initial CRRT may be associated with some improvement in long-term quality of life.^{53,54}

CONCLUSION

Data from several studies have shown that the choice of initial mode of RRT may not have an impact on length of ICU stay or short-term mortality. Hence, other factors must decide which mode of RRT to be initiated for a particular patient. In a country like India, limited healthcare resources and cost of therapy are always important factors to consider whenever taking such decisions. Even though several studies have shown that CRRT may be more expensive compared to IRRT, when you factor in long-term costs, it might be more cost-effective. Reduced long-term dialysis dependence and better quality of life associated with CRRT, may make it a better option. Moreover, several measures, like better manpower management, choosing the right anticoagulation, and reducing the rate of dialysis dose delivery, may all significantly reduce the initial costs of CRRT and make it a much more financially viable.

REFERENCES

1. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3365-70.
2. Levy EM, Viscoli CM, Horwitz RJ. Effect of acute renal failure on mortality. A cohort analysis. *JAMA.* 1996;275:1489-94.
3. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA.* 2005;294:813-8.
4. Cole L, Bellomo R, Silvester W, et al. A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system. *Am J Respir Crit Care Med.* 2000;162:191-6.

5. Majumdar A. Sepsis-induced acute kidney injury. *Indian J Crit Care Med.* 2010;14:14-21.
6. Bellomo R, Ronco C, Kellum JA, et al.; Acute Dialysis Quality Initiative workgroup. Acute renal failure: Definition, outcome measures, animal models, fluid therapy and information technology needs. The second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care.* 2004;8:R204-12.
7. Hou SH, Bushinsky DA, Wish JB, et al. Hospital-acquired renal insufficiency: a prospective study. *Am J Med.* 1983;74(2):243-8.
8. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* 2002;39(5):930-6.
9. Shusterman N, Strom BL, Murray TG, et al. Risk factors and outcome of hospital-acquired acute renal failure: clinical epidemiologic study. *Am J Med.* 1987;83(1):65-71.
10. Nickolas TL, Barasch J, Devarajan P. Biomarkers in acute and chronic kidney disease. *Curr Opin Nephrol Hypertens.* 2008;17(2):127-32.
11. Case J, Khan S, Khalid R, et al. Epidemiology of acute kidney injury in the intensive care unit. *Crit Care Res Pract.* 2013;2013:479730.
12. Paudel MS, Wig N, Mahajan S, et al. A study of incidence of AKI in critically ill patients. *Ren Fail.* 2012;34(10):1217-22.
13. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* 2009;35(10):1692-702.
14. Bagshaw SM, George C, Bellomo R; ANZICS Database Management Committee. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care.* 2008;12(2):R47.
15. Mani MK. Experience with a program for prevention of chronic renal failure in India. *Kidney Int.* 2005;67:75-8.
16. Agarwal SK, Dash SC, Irshad M, et al. Prevalence of chronic renal failure in adults in Delhi, India. *Nephrol Dial Transplant.* 2005;20:1638-42.
17. Modi GK, Jha V. The incidence of end stage renal disease in India, a population based study. *Kidney Int.* 2006;70:2131-3.
18. Amdur RL, Chawla LS, Amodeo S, et al. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. *Kidney Int.* 2009;76(10):1089-97.
19. Chertow GM, Soroko SH, Paganini EP, et al. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. *Kidney Int.* 2006;70(6):1120-6.
20. Bellomo R. The epidemiology of acute renal failure: 1975 versus 2005. *Curr Opin Crit Care.* 2006;12(6):557-60.
21. Ympa YP, Sakr Y, Reinhart K, et al. Has mortality from acute renal failure decreased? A systematic review of the literature. *Am J Med.* 2005;118(8):827-32.
22. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16(11):3365-70.
23. Prescott GJ, Metcalfe W, Baharani J, et al. A prospective national study of acute renal failure treated with RRT: incidence, etiology and outcomes. *Nephrol Dial Transplant.* 2007;22(9):2513-9.
24. Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? *Crit Care Med.* 2008;36(4 Suppl):S146-51.
25. Chawla LS, Amdur RL, Amodeo S, et al. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int.* 2011;79(12):1361-9.
26. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care.* 2006;10(3):R73.
27. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med.* 2006;34(7):1913-7.
28. Waikar SS, Curhan GC, Wald R, et al. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol.* 2006;17(4):1143-50.
29. Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol.* 2006;17(4):1135-42.
30. Teixeira C, Garzotto F, Piccinni P, et al; for the NEFROlogia e Cura Intensiva (NEFROINT) investigators. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. *Crit Care.* 2013;17(1):R14.
31. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med.* 2009;37(3):1101-20.
32. Ronco C, Zanella M, Brendolan A, et al. Management of severe acute renal failure in critically ill patients: an international survey in 345 centres. *Nephrol Dial Transplant.* 2001;16:230-7.
33. Swartz RD, Messana JM, Orzol S, et al. Comparing continuous hemofiltration with hemodialysis in patients with severe acute renal failure. *Am J Kidney Dis.* 1999;34:424-32.
34. Srisawat N, Laws L, Uchino S, et al. Cost of acute renal replacement therapy in the intensive care unit: results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Study. *Crit Care.* 2010;14:R46.
35. Marshall MR, Ma T, Galler D, et al. Sustained low efficiency daily dialysis (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. *Nephrol Dial Transplant.* 2004;19(4):877-84.
36. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359:7-20.
37. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med.* 2009;361(17):1627-38.
38. Tolwani AJ, Wille KM. Anticoagulation for continuous renal replacement therapy. *Semin Dial.* 2009;22:141-5.
39. Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int.* 2001;60(3):1154-63.
40. Vitale C, Bagnis C, Marangella M, et al. Cost analysis of blood purification in intensive care units: continuous versus intermittent hemodiafiltration. *J Nephrol.* 2003;16(4):572-9.
41. Rauf AA, Long KH, Gajic O, et al. Intermittent hemodialysis versus continuous renal replacement therapy for acute renal failure in the intensive care unit: an observational outcomes analysis. *J Intensive Care Med.* 2008;23(3):195-203.
42. Uchino S, Bellomo R, Ronco C. Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid-base balance. *Intensive Care Med.* 2001;27(6):1037-43.
43. Ronco C, Bellomo R. Dialysis in intensive care unit patients with acute kidney injury: continuous therapy is superior. *Clin J Am Soc Nephrol.* 2007;2(3):597-600.
44. Ronco C. Continuous dialysis is superior to intermittent dialysis in acute kidney injury of the critically ill patient. *Nat Clin Pract Nephrol.* 2007;3(3):118-9.
45. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicenter randomized trial. *Lancet.* 2006;368(9533):379-85.
46. Pannu N, Klarenbach S, Wiebe N, et al. Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA.* 2008;299(7):793-805.
47. Bagshaw SM, Berthiaume LR, Delaney A, et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med.* 2008;36(2):610-7.
48. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. *Lancet.* 2000;356(9223):26-30.
49. Silvester W, Bellomo R, Cole L. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. *Crit Care Med.* 2001;29(10):1910-5.
50. Olivier E, Antoine S, Sean MB, et al. Economics of dialysis dependence following renal replacement therapy for critically ill acute kidney injury patients. *Nephrol Dial Transplant.* 2015;30:54-61.
51. Schneider AG, Bellomo R, Bagshaw SM, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med.* 2013;39:987-97.
52. Wald R, Shariff SZ, Adhikari NK, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. *Crit Care Med.* 2014;42:868-77.
53. De Smedt DM, Elseviers MM, Lins RL, et al. Economic evaluation of different treatment modalities in acute kidney injury. *Nephrol Dial Transplant.* 2012;27(11):4095-101.
54. Ethgen O, Schneider AG, Bagshaw SM, et al. Economics of dialysis dependence following renal replacement therapy for critically ill acute kidney injury patients. *Nephrol Dial Transplant.* 2015;30(1):54-61.

Section 6

Neurology

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Declaration of Brain Death in India: Current Status

Dinesh K Singh, Gaurav Jain

INTRODUCTION

Death declaration is a medicolegal debate. In earlier days, the determination of death simply involved the documentation of loss of vital signs. However, modern life support systems now maintain the cardiorespiratory functions long enough, even after the brainstem functions have terminated irreversibly. Thus, the current concept of cardiopulmonary definition of death has lost its real meaning in favor of the brain death. At present, brain death is defined as an irreversible cessation of all functions of the brain, including the brainstem. The three essential prerequisites for brain death include apnea, absence of brainstem reflexes, and coma. The lack of awareness and the medicolegal doubts further delays the prompt declaration of brain death, and adds to the needless load on the life supporting capabilities of medical care facilities. In this segment, the authors would highlight the historical aspects, anatomical and physiological basis, current controversies, and the recommendations regarding the diagnoses of brain death in India.¹

HISTORICAL INSIGHT^{1,2}

The medicolegal and ethical aspects of brain death, though closely interrelated to organ transplantation, are unfamiliar to common people, even to majority of healthcare physicians in India. In early 90s, the first legal recommendations defining the guidelines for brain death certification were passed by Indian parliament, similar to the United Kingdom laws related to human organ donation. It included two acts, commonly described as the "Transplantation of Human Organs Act, 1994" (THO Act) and the "Transplantation of Human Organs Rules, 1995" (THO Rules). Recent amendments in the above act (THO Amendment, 2011) have included four other specialties, eligible for certifying brain dead (Box 1). The same amendments have been notified recently under the "Transplantation of Human Organs and Tissues Rules (THOTR), 2014".

Most of the Indian states have enacted these laws with an exception of a few. These are empowering legislation as far as deceased donor transplantation is concerned. However, till recently, there was no established procedure or guideline to deal with situations that arises when brain death occur in hospitals that are not registered under THO Act and Rules, even when the families wish to give consent to donate the organs of their deceased family member. Maharashtra has been the first state to pass a legislature (Resolution, 2012) in this aspect, laying down recommendations and procedures for declaration of brain death by any healthcare facility of the State. This notification has highlighted the accountability of hospitals registered under the THO Act, 1994 as authorized transplant centers. As majority of brain death cases occur in nontransplant hospitals, it has made "Director of Health Services" accountable for registration of all hospitals having a facility of an operation theater and intensive care unit, and has defined them as "Non-Transplant Organ Retrieval Centers" (NTORC). These healthcare facilities have been permitted to certify brain death as per guidelines. They may also perform organ retrieval for therapeutic purposes but are prohibited from performing actual transplantation. It is now obligatory for all NTORCs and transplant centers in the State to certify and notify the brain death cases to "Zonal Transplantation Coordination Committee".

Box 1: Details of Amendments made in Transplantation of Human Organ Act 2011 and Transplantation of Human Organs and Tissues Rules, 2014

- Surgeon/Physician/Anesthetist/Intensivist may be a member of medical board for brainstem death certification
- Mandates to have a duly signed, written approval from the parents of the deceased or near relatives (authorized by parents) for any organ retrieval
- "Form 8" (format for brain death certification) has been recategorized as "Form 10", under new rules

Kerala state has also recently mandated the notification of brain dead cases (G.O. No.36/2012), though restricted to medical care facilities registered as Transplant Centers in the state. The Director of Medical Education and Health Services has been directed to periodically organize the awareness workshops on the provisions of such resolution. These are firm initiatives to streamline the system for brain death certification and human organ retrieval. However, a proper medicolegal structure for certification of brain death is still a long way ahead in India in absence of consensus among the different states for having a precise legislature for the above procedure.

ANATOMICAL AND PHYSIOLOGICAL BASIS OF BRAIN DEATH

The brainstem consists of the midbrain, pons, and medulla. It accommodates lower ten cranial nerve nuclei, reticular formation, vital centers like cardiac, respiratory nuclei, and provides passage to nerve bundles from higher centers of consciousness, perception, orientation, eating behavior, and cognition. The functionality of brainstem is examined by observing spontaneous respiratory activity, consciousness, and integrity of cranial nerves. Consciousness is a sense of wakefulness and awareness being regulated by reticular formation in close association with cerebral cortex. Cerebral cortex integrity is determined by assessing electrical activity of brain by electroencephalogram (EEG), lack of verbal response, and absence of spontaneous or coordinated eye movements. Common causes of brain injury frequently precipitating irreversible coma comprise trauma, hemorrhage, ischemic stroke, or hypoxic-ischemic encephalopathy. Any damage to the neuronal tissue leads to cerebral edema, hydrocephalus, and rise in intracranial pressure (ICP). This in turn reduces the cerebral perfusion, leading to a vicious cycle if not intervened, precipitates as brain herniation and the brainstem is irreversibly rendered nonfunctional.

CURRENT RECOMMENDATIONS (INDIA): WHO SHOULD DECLARE BRAINSTEM DEATH?³⁻¹⁰

In India, the THO Act (1994) and the THO Rules (1995), are the only legislations wherein brain death certification procedures have been laid down, though a minor addition has been made in THO Amendment, 2011. The "Form 8" of the above laws has been documented as brain death certification format, which has to be utilized for any official purpose. It has recently been recategorized as "Form 10" under the rule 5(4c) and 5(4d) of "THOTR, 2014" without any further modification.

The brain death certification requires two serial medical examinations, carried out by a team of predefined doctors at a minimal interval of 6 hours to make sure that there has been

no observer error and perseverance of the clinical condition is documented. The final decision is made by a board of medical experts, defined as "Brain Stem Death Certifying Board" (BSD) based on the examination findings and the tests prescribed therein. The THO Act and Rules prescribe a board of BSD experts consisting four doctors, defined as follows:

1. Medical expert no. 1 is a registered medical practitioner (RMP), who is incharge/head of the hospital where brain death has to be certified. Registered medical practitioner is defined as an allopathic doctor with MBBS or equivalent degree registered under the Medical Council of India Act
2. Medical expert no. 2 is an independent RMP nominated from the panel of names approved by the appropriate authority. The panel of names has to be proposed by the Medical Superintendent/Director of the hospital through the District Medical Officer to the Core Committee for Cadaver Transplantation (CCCT) and on clearance is then adopted as the panel from which an RMP is selected for each brain death certification. Each healthcare facility may elect a separate panel of names for this responsibility
3. Medical expert no. 3 is an RMP, "neurologists/neurosurgeon" by specialty, nominated from the panel of names approved by the appropriate authority. Again, a similar procedure is followed to get the clearance from CCCT and thereafter, one specialist as in the category therein is nominated for each brain death certification. Each healthcare facility may adopt its own practice for this responsibility. A recent amendment under THOTR, 2014 has permitted the nomination of a surgeon/physician/anesthetist, or intensivists, if a neurosurgeon or neurologist is unavailable. This is aimed to ease the pressure on neurologists/neurosurgeons, thus improving the certification rate and organ pool.
4. Medical expert no. 4 is an RMP treating the deceased person (no approval is required from the appropriate authority for this expert).
5. Expert no. 2 and 3 should not be a part of the hospital where the brainstem death patient is being treated
6. The 1st and 2nd deceased medical examination as defined in the THO Rules is to be conducted by no. 2 and 3 medical experts from the panel approved by the appropriate authority.

CURRENT RECOMMENDATIONS (INDIA): CRITERIA FOR DIAGNOSING BRAINSTEM DEATH¹¹⁻¹⁶

All the observations made during both clinical examinations including the patient details, underlying diagnosis, and the date of onset of illness and irreversible coma, have to be documented on the prescribed format (Form 8) and duly signed by the team of prescribed medical experts. The medical team must make meticulous efforts to inform the

first degree relative about the procedure for determining brain death and ask about willingness for deceased organ donation (if diagnosis is confirmed) which should be documented. The THOTR (2014) now mandates a duly signed-written approval from the parents of the deceased or near relatives (authorized by parents) for any organ retrieval. This is to ensure willingness of the deceased relatives for organ donation.

The clinical diagnosis of brain death requires three criteria to be fulfilled which are detailed as follows:

1. A state of irreversible coma having clinical evidence of an acute central nervous system catastrophe that is compatible with the clinical diagnosis of brain death. Any cause of reversible coma including drugs, toxins, hypovolemic shock, hypothermia, metabolic or endocrine disorders, etc., have to be ruled out
2. All brainstem reflexes should be absent during complete neurological examination involving following tests:
 - Absent pupillary reflex (to direct and consensual light): Pupils need not be equal or dilated. Confounding factors, such as eye trauma, cataracts, dopamine, atropine, scopolamine, or monoamine oxidase inhibitors, should be ruled out
 - Absent corneal reflex: It is performed by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen
 - Absent oculoccephalic reflex (Doll's head eye maneuver): It is defined as the absence of conjugate deviation of eyes to the opposite side when head is fully rotated to one side. It is performed only when there is no documented fracture or instability of the cervical spine
 - Absent oculovestibular reflex: It is performed by irrigating each ear with 50 mL of ice water (caloric testing) after the patency of the external auditory canal is confirmed and the head is elevated to 30°. Positive response includes either nystagmus or deviation of eyes. Movement of the eyes should be absent during 1 minute of observation. Both sides are tested at an interval of several minutes
 - Absent pharyngeal (gag) reflex: Pharynx is stimulated by a tongue blade or suction device
 - Absent tracheal (cough) reflex: The suction catheter should be inserted into the trachea and advanced to the level of the carina to be followed by 1 or 2 suctioning passes
 - No motor response to stimulation within any cranial nerve distribution, including face, limb, and trunk (e.g., absence of facial movement to supraorbital pressure)
3. Apnea: Patient should be on invasive mechanical ventilation because of the absence of spontaneous respiratory drive. All reversible causes of apnea including neuromuscular blocking agents, acid-base electrolyte disorders, and intoxication, should be ruled out
4. Whole of the above examination has to be repeated after minimum interval of 6 hours. In pediatric patients (<12 years of age) the time interval may be increased depending on the opinion of the experts
5. Apnea test: Absence of respiratory drive has to be further confirmed by performing "apnea test".

Current Recommendations (India): Apnea Test

- **Timing:** The first apnea test should be performed only after 4 hours of documentation of the coma associated with absence of brainstem reflexes. In the case of anoxic brain damage, this period should be delayed to 12 hours
- **Prerequisite:** Patient should have a core body temperature above 36°C, euvolemia, eucapnia (PaCO₂ 35–40 mmHg), a systolic blood pressure (SBP) ≥90 mmHg, absence of hypoxia, and no prior evidence of carbon dioxide retention
- **Preparation:** The patient should be hyperoxygenated with 100% oxygen for 15 minutes (preoxygenation to PaO₂ >200 mmHg) while still on ventilator, prior to disconnection. The medical expert involved in certifying the brain death should be present during the ventilator removal, to document the presence of apnea, if observed. A blood gas analysis or the end-tidal carbon dioxide trends should be utilized to ascertain the adequacy of baseline variables prior to performing the test
- **Procedure:** After disconnecting the ventilator, patient is placed on 100% oxygen delivered via a catheter placed close to carina through the endotracheal tube, with 6 L/min continuous oxygen flow for a variable period of observation, usually 3–8 minutes. During this period, the patient is observed for any respiratory movements (defined as abdominal or chest excursions), SpO₂, SBP, and electrocardiographic changes. If respiratory efforts are observed, test is considered negative. The procedure is aborted if the patient develops cardiac arrhythmia, SpO₂ values falls <90% or SBP becomes <90 mmHg. Such patients are immediately connected to the ventilator and blood gas analysis is repeated. Similar protocol is followed after the period of observation, if no respiratory efforts are observed
- **Results:** Test is considered positive if the post-test blood gas values reveal arterial PaCO₂ ≥55 mmHg or rise of ≥15 mmHg over the baseline values. The test is considered inconclusive for any lower PaCO₂ values. Test may be repeated for a longer period (10–15 min) for all such patients who are hemodynamically stable; otherwise confirmatory tests may be utilized, if advocated.

Current Recommendations (India): Confirmatory tests¹⁷⁻²²

The certification of brain death is purely based on the clinical examination in India. Neuroimaging evidence or the other

ancillary tests are not a diagnostic prerequisite nor are medicolegal necessity. If there is any disagreement or doubt among the members of medical panel, these tests may be advised to confirm the diagnosis. The various confirmatory tests advocated across the globe are cerebral angiography, EEG, transcranial Doppler, nuclear brain imaging (technetium-99m scan), or somatosensory/brainstem auditory/visual evoked potentials. Computed tomographic or magnetic resonance angiography, though included by some guidelines, have no consensus.

- Cerebral angiography: Especially a four-vessel angiogram, demonstrating the absence of intracerebral filling at the level of the carotid bifurcation or circle of Willis, this remains the gold standard ancillary test among the various prescribed techniques
- Electroencephalogram: In spite of some major constraints with acid base disorders, hypothermia, etc., EEG still remains the most popular supplementary test for confirmation of brain death worldwide. The diagnosis is confirmed by documenting the absence of electrical activity during at least 30 minutes of EEG recording
- Radionuclide technetium-99 m scan: It confirms the diagnosis by demonstrating absence of isotope uptake in brain parenchyma (hollow skull phenomenon) in brain death
- Somatosensory evoked potentials: Bilateral absence of N20-P22 response on median nerve, nasopharyngeal stimulation, etc. has also been advocated in the evaluation of brain death
- Transcranial doppler: Brain death is confirmed by demonstrating small systolic peaks in early systole without any diastolic flow, or reverberating flow in the cerebral circulation indicating very high vascular resistance associated with increased ICP. On account of skull thickness, nearly 10% of patients may not have temporal insonation window, a major limitation in using Doppler signals for the diagnosis of brain death.

GUIDELINES FOR BRAIN DEATH: CONTROVERSIES²³⁻²⁵

Despite worldwide consensus of utility of brain death, variation in concept, clinical guidelines, and ancillary tests persist throughout the globe. Many guidelines do not consider pupillary dilation and equality as a necessity. There is also wide variation in the acceptance of oculocephalic reflex considering its lower sensitivity in brain injury patients. Other guidelines do not require a second medical examination, and if at all performed, there is lack of unanimity on when it should be repeated. The qualification, experience, and number of medical experts required for brain death certification also vary widely. Core temperature threshold for performing apnea test also vary widely from 32.2 to 36.0°C among different guidelines. There are also differences in interpretation of apnea test, with many

considering a specified PaCO₂ target, while others only document disconnection of ventilator for a specified period to observe respiratory movements only.

In India, it is brainstem death and not brain death which is a legal necessity. Hence, theoretically, it is possible that a patient is certified brain dead as per rules, although the EEG may be demonstrating some cortical activity. Furthermore, the current Indian legislature is silent on two other scenarios. First, if the relatives deny for the organ donation in a brainstem dead certified patient, whether the life support systems can be disconnected and patient be certified dead. Second, if the relatives request to have some time to decide about the organ donation during which patient develops cardiac arrest, the time to be documented for death declaration is unclear.

CONCLUSION

The distinction and unanimity on the concept of brain death is the need of the hour, considering the wide shortage of human organ donations and acute rise in the medicolegal cases against the medical fraternity, all across the globe. Wide variations in the clinical guidelines and practical inconsistencies closely relates to the nonacceptance and unawareness on such an important aspect of medical care. The existing laws need a peer refinement and updation to deal with the newer challenges encountered during the clinical practice, taking advantage of the advancement in the medical investigations. Uniform guidelines and updated laws will not only promote the wide acceptability and applicability of brain death certification, but will also ensure better availability of potential organ donors.

REFERENCES

1. Baron L, Shemie SD, Teitelbaum J, et al. Brief review: History, concept and controversies in the neurological determination of death. *Can J Anaesth*. 2006;53:602-8.
2. Greer DM, Varelas PN, Haque S, et al. Variability of brain death determination guidelines in leading US neurologic institutions. *Neurology*. 2008;70:284-9.
3. Government of India. Ministry of Law, Justice and Company Affairs (Legislative Department), New Delhi. The Transplantation of Human Organs Act, 1994. Central Act 42 of 1994. [online] Available from: <http://www.health.bih.nic.in/Rules/THOA-1994.pdf>.
4. Government of India. Ministry of Law, Justice and Company Affairs (Legislative Department), New Delhi. The Transplantation of Human Organs (Amendment) Act, 2011 (No. 16 of 2011). [online] Available from: <http://www.mohanfoundation.org/THO-amendment-act-2011.pdf>.
5. Government of India. Ministry of Law, Justice and Company Affairs (Legislative Department), New Delhi. The Transplantation of Human Organs Rules, 1995 (GSR NO. 51(E), dr. (1995 Feb 04) [As amended vide GSR 571(E), 2008].
6. Government of India. Ministry of Law, Justice and Company Affairs (Legislative Department), New Delhi. Transplantation of Human Organs (Amendment) Rules, 2008. [online] Available from: <http://www.health.bih.nic.in/Rules/THO-A-Rules-2008.pdf>. Last accessed July, 2014.
7. Government of India. National Organ and Tissue Transplant Organization (NOTTO), Directorate General of Health Services, Ministry of Health and Family Welfare, New Delhi. Form 10. [online] Available from: <http://notto.nic.in/WriteReadData/Portal/Images/FORM10.pdf>.

8. Government of India. National Organ and Tissue Transplant Organization (NOTTO), Directorate General of Health Services, Ministry of Health and Family Welfare, New Delhi. Transplantation of Human Organs and Tissues rules, 2014. [online] Available from: <http://notto.nic.in/act-end-rules-of-thoa.htm>.
9. Government of Kerala. Health & Family Welfare Department – Transplantation of Human Organs –Declaration of brain death mandatory in Government and Private Hospitals in the State – Procedure for declaration of brain death. (G.O (MS)No.36/2012/H&FWD Dated, 04.02.2012). [online] Available from: www.aarogyakeralam.gov.in/docs/go/25.pdf.
10. Government of Maharashtra, Public Health Department, Government Resolution No.MAP2012/C.R.289/AROGYA-6. Mumbai: Mantralaya; 2012. [online] Available from: <https://www.maharashtra.gov.in/Site/Upload/Government%20Resolutions/English/201209141533080800.pdf;201209141531450800.pdf;201209141533590800.pdf>.
11. Dhanwate AD. Brain stem death: A comprehensive review in Indian perspective. *Indian J Crit Care Med.* 2014;18(9):596-605.
12. Goila AK, Pawar M. The diagnosis of Brain Death. *Indian J Crit Care Med.* 2009;13(1):7-11.
13. Molina DK, McCutcheon JR, Rulon JJ. Head injuries, pentobarbital, and the determination of death. *Am J Forensic Med Pathol.* 2009;30:75-7.
14. Reddy KSN, Murty OP. The Essentials of Forensic Medicine and Toxicology. 27th edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2008. p. 119.
15. Sethi NK, Sethi PK. Brain Death: Implications in India. *JAPI.* 2003;5:910-1.
16. Shroff S, Navin S, Abraham G, et al. 'Ramachandra protocol' for organ donation. *Antiseptic.* 1997;94:73-4.
17. De Tourcharinoff M, Hantson P, Mahieu P, et al. Brain death diagnosis in misleading conditions. *QJM.* 1999;92:407-14.
18. Ducrocq X, Braun M, Debouverie M, et al. Brain death and transcranial Doppler: Experience in 130 cases of brain dead patients. *J Neurol Sci.* 1998;160:41-6.
19. Schwab RS, Potts F, Bonazzi A. EEG as an aid in determining death in the presence of cardiac activity ethical, legal, and medical aspects. *Electroencephalogr Clin Neurophysiol.* 1963;15:147-8.
20. Su Y, Yang Q, Liu G, et al. Diagnosis of brain death: Confirmatory tests after clinical test. *Chin Med J (Engl).* 2014;127:1272-7.
21. Wig N, Gupta P, Kailash S. Awareness of brain death and organ transplantation among select Indian population. *J Assoc Physicians India.* 2003;51:455-8.
22. Young GB, Shemie SD, Doig CJ, et al. Brief review: The role of ancillary tests in the neurological determination of death. *Can J Anaesth.* 2006;53:620-7.
23. Wijdicks EF, Varelas PN, Gronseth GS, et al. American Academy of Neurology. Evidence-based guideline update: Determining brain death in adults: Report of the quality standards subcommittee of the American academy of neurology. *Neurology.* 2010;74:1911-8.
24. Wijdicks EF. Brain death worldwide: Accepted fact but no global consensus in diagnostic criteria. *Neurology.* 2002;58:20-5.
25. Wijdicks EF. Brain Death. Philadelphia: Lippincott Williams and Wilkins; 2001. p.175.

Blood Pressure Management in Stroke

Susruta Bandyopadhyay

INTRODUCTION

Hypertension is a major risk factor for all strokes. Although control of chronic hypertension remains a necessary intervention for prevention of stroke, the role of control of blood pressure (BP) in acute strokes is still unclear. Three quarters of patients with acute ischemic stroke have elevated BP at presentation, of which about half have a history of hypertension. Among the patients with acute intracerebral hemorrhage (ICH), 46-75% present with high systolic blood pressure (SBP). The cause of this acute hypertension during stroke may be due to the stroke itself or from pain, discomfort (e.g., from urinary retention), anxiety, etc. Blood pressure declines spontaneously over the first week after stroke onset and returns to prestroke levels in two thirds of patients.^{1,2}

Persistent elevation of BP in acute stroke can increase the size of hematoma in ICH, cause edema with increased intracranial pressure (ICP) at the site of the stroke, or cause hemorrhagic transformation of infarctions. On the other hand, a rapid and substantial reduction in BP may reduce cerebral perfusion pressure (CPP) and increase ischemic areas. In fact, the increased BP in acute strokes may be a reflex response to increase CPP. Hence, the treatment of hypertension in acute stroke remains an evolving science. Physicians must approach with prudence while managing hypertension in acute strokes, keeping in mind:

- The type of stroke (ischemic/hemorrhagic)
- The level of hypertension
- The patient's past history of hypertension
- The physiology of brain circulation in acute stroke.

CEREBROVASCULAR PHYSIOLOGY³⁻⁵

The general formula for cerebral blood flow (CBF) is as follows:

$$CBF = (ABP - ICP) / CVR$$

(ABP = Arterial blood pressure, CVR = Cerebral vascular resistance)

CPP = ABP – ICP or CVP (whichever is higher)
(CVP = Central venous pressure)

Since neurons are highly dependent on adequate substrate delivery in order to maintain viability, CBF is tightly controlled. The brain maintains a constant CBF at approximately 50 mL/100 g/min despite large changes in BP and CPP. When BP increases, cerebral vessels constrict and CVR increases in order to maintain a constant flow. When BP decreases or ICP increases, the vessels dilate and CVR decreases to keep CBF constant. The cerebral autoregulation is effective in a mean arterial pressure (MAP) range of 50-150 mmHg in normotensive individuals. The relationship of CBF with systemic arterial pressure remains essentially nonlinear. That is to say the CBF depends on ABP, but does not increase or decrease in proportion to the increase or decrease in ABP. This nonlinear relationship between ABP and CBF is due to several associated factors, like autoregulation of the intracerebral blood vessels, and an intricate relationship between cardiovascular and cerebral vascular systems, ICP, autonomic nervous system and neurohumoral transmitters.

When BP falls below the lower limit of autoregulation, CBF becomes completely dependent on CPP and thus, systemic blood pressure. The CBF, in that case, becomes compromised.

The three main systems which control CBF are:

1. Cardiovascular system: The CBF depends on the systemic blood pressure which in turn depends on cardiac output as well as systemic vascular resistance. CBF is again related to cardiac output independent of the systemic blood pressure. Although, as already pointed out, the relationship between systemic arterial pressure and CBF remains nonlinear.
2. Intracranial pressure: As the skull in a rigid structure any rise in the pressure in any of the compartments of the brain, like vascular (raised ABP, neck position), cerebrospinal fluid (hydrocephalus) or brain parenchyma (trauma, ICH, space-occupying lesion), will raise the ICP and can decrease the CPP, which in turn will reduce CBF.

3. Cerebral vascular system: There is a considerable regulation of CVR, mainly at the level of intracerebral arterioles, but also at the level of arteries, veins and capillaries. This autoregulation allows the brain to maintain satisfactory CBF over a wide range of ABP. The cerebral autoregulation is mediated by mediators which may be carried by blood (like carbon dioxide), produced locally at synapses or released by autonomic nerves. Dynamic cerebral autoregulation is the physiologic process that maintains CBF relatively constant in the face of beat-to-beat BP changes. Static cerebral autoregulation refers to CBF adjustments in response to more prolonged BP changes and is a measure of the overall efficiency of the system.⁶

Normal cerebral cortical blood flow is 50 mL/100 g tissue per minute. If this falls below 20 mL/100 g/min, there is impairment of the neuronal tissue, but still they remain salvageable. If the blood flow falls below 10 mL/100 g/min, there is irreparable damage to the neuronal tissues within a few minutes.

EVIDENCE OF INFLUENCE OF THE BLOOD PRESSURE ON THE OUTCOME OF ACUTE STROKES

Lowering BP in people suffering from chronic hypertension reduces the risk of stroke. Epidemiological studies have shown that for each 10 mmHg lower SBP, there is a decrease in risk of stroke of approximately one-third in persons aged 60–79 years. This association continuous to levels of at least 115/75 mmHg and is consistent across gender, regions, stroke subtypes, and for fatal and nonfatal events. Lowering diastolic blood pressure (DBP) was once the main target to achieve reduction of stroke and other cardiovascular event, but SBP has now become the target. As recently shown, even the elderly with sustained SBP elevation may gain from BP reduction in relation to less fatal or nonfatal stroke, death, and heart failure.

Although the role of longer-term BP control to improve outcomes in patients with stroke is undisputed, BP management immediately after a stroke remains controversial.

INFLUENCE OF HIGH SYSTOLIC BLOOD PRESSURE ON ACUTE INTRACEREBRAL HEMORRHAGE

Acute rise in BP after an ICH occurs in 46–75% of patients. A serious concern in the setting of intracerebral hemorrhage is that BP elevation could result in hematoma expansion, increase in surrounding edema, and early rebleeding into the brain. There is growing evidence supporting a relationship between hematoma volume and poor outcome in intracerebral hemorrhage. Although the increase in BP is a major risk factor for intracerebral hemorrhage, high BP during acute stroke is not a consistent predictor of hematoma

growth. Also, it has been reported that acute intracerebral hemorrhage can evolve without a perihematomal ischemic penumbra.⁶ In the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH study (a prospective, multicenter observational study enrolling 211 patients with ICH from 10 Japanese stroke centers), it was found that the mean SBP was higher in patients with unfavorable outcomes [139 (134–143) mmHg] than with favorable [137 (131–141) mmHg] outcomes ($p = 0.012$). It was also observed that every 10 mmHg increment of mean achieved systolic blood pressure (aSBP) was associated with a 4.5-fold increase in neurological deterioration, a 1.8-fold increase in hematoma expansion, and a 2-fold increase in unfavorable outcome after multivariate adjustment.

In another European trial of 117 patients of early onset supratentorial ICH (onset <6 h) and high SBP, which was defined by the proportion of time when SBP was >180 mmHg and/or MAP >130 mmHg, was associated with hematoma growth. Both high SBP and BP variability were associated with early neurological deterioration. On the other hand, in a pooled analysis of 218 patients within 3 hours of the onset of symptoms, hematoma volume was measured at presentation and 20–24 hours later. Percentage hematoma growth, initial ICH volume, Glasgow Coma Scale (GCS) score, and presence of intraventricular hemorrhage were all associated with increased mortality; however, BP was not.⁴ In patients with intracerebral hemorrhage, excessive reduction of BP may result in a new ischemic stroke or perihematomal ischemia. In that case, a marked reduction in BP could be followed by a significant decrease in blood flow to penumbra zone.⁶ The argument against lowering BP in acute ICH is based on the possible existence of a perihematomal ischemic zone. Particularly, chronic hypertensives (due to a shift in the autoregulatory curve) and patients with increased ICP (due to lowered CPP) may develop cerebral ischemia if BP is acutely lowered. Recent studies, however, indicate that low blood flow around the hematoma may be a consequence of reduced cerebral metabolism in this area rather than a primary reduction of blood flow.⁴

INFLUENCE OF THE HIGH SYSTOLIC BLOOD PRESSURE ON ACUTE ISCHEMIC STROKES

High BP (>140/90 mmHg) is seen in 75% of patients with acute ischemic stroke. The reasons for acute hypertensive response in the setting of acute ischemic stroke are still not very well understood.

The first International Stroke Trial found a “U-shaped” relationship between SBP (measured, on average, 24 h after stroke) and outcome in patients with ischemic stroke, where both high and low SBP were independently associated with poor outcome. In this trial, early death increased by 17.9% for every 10 mmHg below 150 mmHg of SBP ($p < 0.0001$), and by 3.8% for every 10 mmHg above 150 mmHg ($p = 0.016$). Also,

the recurrence of stroke within 2 weeks increased by 4.2% for every 10 mmHg increase in SBP ($p=0.023$). Early recurrence of stroke was associated with unfavorable outcome, thus linking BP at admission with increased rate of death or dependency at 6 months. The lowest frequency of poor outcome occurred in patients with a baseline SBP of 140–179 mmHg, with the nadir around 150 mmHg.

Mortality possibly caused by brain edema was independently associated with high SBP ($p=0.004$). On the other hand, a low SBP was associated with severe stroke (total anterior circulation syndrome). The Virtual International Stroke Trials Archive (VISTA) collaboration suggested that large variability and high levels of SBP in the hyperacute stages of ischemic stroke were associated with high incidence of severe neurological events and major neurological disability outcome.

INTERVENTIONS FOR ALTERING BLOOD PRESSURE IN ACUTE STROKE

Intracerebral Hemorrhage

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) was a small, pilot trial of 404 patients, mostly hypertensives with mild to moderate ICH and an initial SBP of 150–220 mmHg. Patients were randomized to early intensive treatment with intravenous antihypertensive drugs or as per recommended existing guideline, within 6 hours of the acute event. The goal of the intensive antihypertensive treatment was to lower SBP to <140 mmHg within 1 hour of randomization and maintain that level for the next 7 days or until hospital discharge. The goal for the guideline group was to reduce SBP to <180 mmHg. For this purpose, oral antihypertensives or topical nitrates were prescribed to all participants within 7 days of the acute stroke. The lower limit of SBP to withdraw intravenous antihypertensive drugs was 130 mmHg. In both groups, the combination of a diuretic and an angiotensin-converting enzyme inhibitor was prescribed. The main results of INTERACT suggested that in patients with spontaneous intracerebral hemorrhage, the rapid lowering of SBP attained with the intensive protocol is reasonably efficient and safe. Additionally, intensive antihypertensive treatment seemed to lessen the growth of intracerebral hemorrhage when compared with a more conservative BP management. However, there were no difference between both antihypertensive strategies on the mortality and dependency, or in stroke recurrence at 3 months.

A small trial (211 patients) on ICH with SBP ≥ 180 mmHg and presenting within 3 hours of the onset of symptoms where the patients were divided into SBP quartiles. The results showed that the patients with lowest mean aSBP quartile had a lower rate of neurological deterioration, hematoma expansion, and unfavorable outcome compared with those in the highest quartile.⁷

The larger version of the INTERACT trial, INTERACT II included 2,839 patients with mild spontaneous intracerebral hemorrhage and SBP in the range of 150–220 mmHg up to 6 hours (median, 4 h) after stroke onset. The patients enrolled had a score greater than 5 on the GCS. At 1 hour after randomization, mean SBP was 150 mmHg in the intensive-treatment group and 164 mmHg in the standard-treatment group. The results showed that larger SBP reductions in the acute phase of ICH are associated with lower risks of a poor outcome, defined by the combination of either death or major disability. This relationship is consistent for BP reduction in the hyperacute and acute phases of ICH, and whether the baseline SBP is above or below the conventional SBP target of 180 mmHg. These data reinforce potential beneficial effects of rapid lowering of elevated SBP within the first few hours after presentation, but also for consistent and sustained control of SBP over the subsequent week in ICH, irrespective of SBP level at presentation.

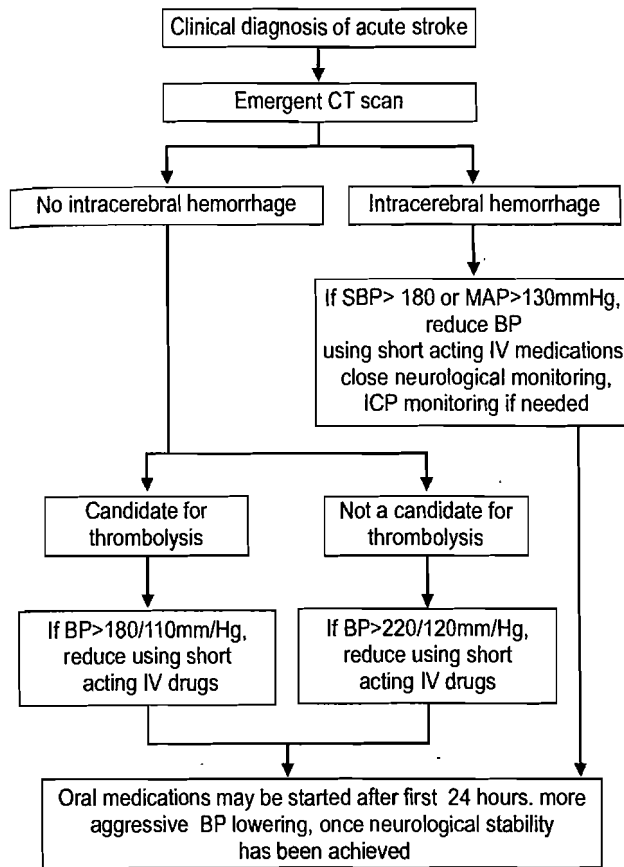
The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT), a multicenter, randomized, prospective study reported that rapid intravenous antihypertensive therapy with labetalol, hydralazine or enalaprilat after moderate volume intracerebral hemorrhagic stroke with an SBP target of <150 mmHg or <180 mmHg within 24 hours, was safe and did not reduce perihematoma CBF in 2-hour period.

Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH II) trial studied 1,000 patients with supratentorial ICH with an SBP of 200.6 ± 27 and GCS score ≥ 5 and presenting within 4.5 hours of symptom onset and was randomized (500 in each group) to intensive treatment group with a target SBP of 110–139 mmHg and a standard treatment group with a target SBP of 140–179 mmHg within 24 hours. The SBP was controlled with intravenous nicardipine, followed by intravenous labetalol, if necessary. There was no difference in primary outcome of death and disability. There were more renal adverse events in the intensive treatment group at 3 months. The patients were treated earlier than INTERACT II trial and they attained their target SBP better.^{8,9}

Acute Ischemic Stroke

The Intravenous Nimodipine West European Stroke Trial (INWEST),¹⁰ an acute ischemic stroke treatment trial testing the therapeutic effects of nimodipine (a calcium channel blocker) as cytoprotective therapy within 24 hours after onset of ischemic stroke, found that prominent reduction in BP in patients randomized to IV nimodipine was associated with worse clinical outcomes at 21 days. Statistically, significantly higher rates of death and disability were seen in association with a decrease in DBP >20% or a DBP <60 mmHg.

In the candesartan for treatment of acute stroke (SCAST) trial,¹¹ 2,029 patients presenting within 30 hours of an acute stroke were randomly allocated to receive candesartan versus placebo. Blood pressures were significantly lower in



BP, blood pressure; SBP, systolic blood pressure; ICP, intracranial pressure; MAP, mean arterial pressure; IV, intravenous.

FLOWCHART 1: Treatment of acute hypertensive response among patients with stroke and stroke subtypes. Based on the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator prethrombolytic protocol for patients with acute ischemic stroke, for short-term blood pressure (BP) management by emergency medical services without delaying early diagnosis and differentiation. The Emergency Medical Services BP management practices vary considerably in the absence of distinction between ischemic stroke and intracerebral hemorrhage. Based on recommendations of the America Stroke Association (ASA), Stroke Council, and/or European Stroke Initiative. The recommended BP treatment threshold is similar to the existing ASA and European Stroke Initiative recommendations for patients with ICH. Based on recommendations of Seventh Report of the Joint National Committee and the Acute Candesartan Cilxetil Therapy in Stroke Survivors protocol

the candesartan group compared to placebo within the 7-day treatment period. At 6-month follow-up, the candesartan group had higher risk of poor functional outcome. The study concluded BP lowering with candesartan showed no benefit in patients with acute stroke. If anything, the evidence suggested a harmful effect.

The Acute Candesartan Cilxetil Therapy in Stroke Survivors (ACCESS) study aimed to evaluate the safety of modest lowering of BP with candesartan in the early treatment of stroke. The study showed that, in the absence of BP lowering, candesartan treatment for 7 days started within 24 hours of stroke onset reduced the cumulative 12-month mortality rate (7.2% and 2.9% for placebo and candesartan,

respectively) and vascular events (18.7% and 9.8% for placebo and candesartan, respectively). The study concluded that candesartan is safe to use in the prevention and treatment of acute stroke and may provide therapeutic benefits. However, there was no difference in BP between the candesartan and placebo arms of this trial, neither within the first 7 days nor 12 months.

Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS).¹² In this multicenter, prospective, randomized, double-blind, placebo-controlled, titrated-dose trial, patients with acute stroke were divided into two groups. The first group consisted of patients who had symptom onset less than 36 hours and hypertension (SBP > 160 mmHg), and the second group had patients with symptoms onset < 12 hours and hypotension (SBP < 140 mmHg). Patients were allocated to either the pressor or the depressor arm depending on BP at randomization. The pressor arm was closed early because of problems with recruitment. In the depressor arm, oral and sublingual lisinopril and oral and intravenous labetalol did not increase the likelihood of early neurological deterioration. The study was not sufficiently powered to detect a difference in disability or death at 2 weeks. However, the 3-month difference in mortality favored active treatment is of interest, although care must be taken in interpretation of the results.

In the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS),¹³ 4,071 patients who presented within 48 hours of onset of stroke and had elevated SBP were randomly assigned to receive antihypertensive treatment or to discontinue all antihypertensive medications during hospitalization. The study concluded that BP reduction had no effect on the incidence of death and major disability at 14 days or at hospital discharge when compared with the absence of hypertensive medications in patients who presented with an acute ischemic stroke and did not receive tissue plasminogen activator (tPA). There was also no difference in the outcome of death or major disability at 3 months between the two groups.

Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): This United Kingdom trial recruited adult patients who were taking antihypertensive drugs and were enrolled within 48 hours of stroke and the last dose of antihypertensive drug. Patients were randomly assigned to either continue or stop preexisting antihypertensive drugs for 2 weeks. Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months. Lower BP levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events.

Efficacy of nitric oxide in stroke (ENOS), with or without continuing antihypertensive treatment, for management of high BP in acute stroke, enrolled 4,011 patients with either ischemic (83%) or hemorrhagic (15.6%) stroke. The mean SBP of the patients was 167 mmHg (BP range 140–220

mmHg). The patients were then randomized to receive glyceryl trinitrate patches to bring down the BP, or not to receive glyceryl trinitrate patches. If the patient was on any antihypertensive medicine prior to the event, he/she was also randomized to continue or discontinue it. There was no difference in functional outcome after 30 days.

Patients with acute ischemic stroke who receive thrombolysis usually have transient acute hypertensive response that resolves after recanalization. However, prior to receipt of thrombolysis, high BP is associated with an increased incidence of intracranial hemorrhage. Results of the Australian Streptokinase trial show that patients with ischemic stroke treated with streptokinase who had a SBP >165 mmHg had a higher incidence of intracranial hemorrhage. This was also confirmed by another observational study.

A meta-analysis of 12 major trials was done in patients with acute ischemic stroke which studied 12,703 patients, of which 50% received active intervention to control hypertension. The median time of presentation was 15 hours after the onset of symptoms. The analysis failed to show any difference in outcomes like, death or disability at the end of the study period or at 3 months, vascular events at the end of the study period or at 3 months, recurrent stroke, all-cause mortality, adverse reactions, etc. It also failed to show any extension on the stroke, due to rapid lowering of the BP. The authors surmised that the damage to the penumbra zone of an ischemic stroke due to rapid lowering of BP possibly only occurs in the first 10 hours or less.¹⁴

Another Cochrane Systematic Review was done in 2014, which studied 17,000 patients of acute ischemic stroke and acute hemorrhagic stroke or mixed strokes in 26 trials. The objective of all these randomized control trials was alterations of the BP in acute stroke patients with an objective of favorable outcome. The primary endpoints were combined death or disability/dependency at end of trial (≥ 1 month after stroke). Dependency was defined as the modified Rankin Scale (mRS) >2 (or >3 as available). Secondary endpoints were early case fatality (<1 month), late case fatality (≥ 1 month), early neurological deterioration (<1 month), and late disability or dependency (Barthel Index ≥ 1 month).

Results

There was no overall effect of BP lowering treatment on early death or death at end of trial or dependency irrespective of the type of stroke. Only very early BP lowering (before hospital presentation or within 6 hours of stroke onset) was associated with reduced death or dependency, and improved quality of life. Barthel Index scores (disability scores) were lower if treatment was started within 6 hours of stroke onset. Very early BP lowering (before hospital presentation or within 6 hours of stroke onset) was associated with reduced death or dependency, and improved quality of life.

Immediately continuing prestroke antihypertensive drugs appears to be associated with a worse functional outcome and lower quality of life; hence, it is reasonable to delay treatment until patients are stable and have oral or enteral access to allow safe administration of drugs. All the studied antihypertensive drug classes lowered blood pressure during the period of treatment.¹⁵

Another meta-regression was done on trials to alter BP in acute stroke (both ischemic and hemorrhagic stroke). Involving 37 trials and 9,008 patients, U- and J-shaped relationships were observed between on-treatment BP difference (difference between the mean baseline BP and on-treatment BP) and mortality at the end of 90-day follow-up, and combined death or dependency at the end of follow-up. The lowest odds of early death was observed with a BP difference of 8.1 mmHg. The lowest odds for death or disability at the end of follow-up was seen with a BP difference of about 14.6 mmHg. As per drug classes, worse outcomes were seen with β -blockers.

In an analysis of patients receiving thrombolysis for acute stroke from the "third international stroke trial," 3,035 patients presenting with acute ischemic stroke within 6 hours of onset were randomized to tissue-type plasminogen activator 0.9 mg/kg or open control. Blood pressure was measured at randomization, at start of treatment, and at 30 minutes and 1 and 24 hours after start of treatment, and the use of BP lowering treatment during the first 24 hours was recorded. High baseline BP and high BP variability during the first 24 hours were associated with higher numbers of early adverse events and early deaths and the differences were statistically significant. However, a large decline in BP and use of BP lowering treatment was associated with a reduced risk of poor outcome in 6 months. This was observed irrespective of whether the patient received thrombolysis or not.^{16,17}

THE GUIDELINES¹⁸⁻²¹

- For ICH: American Heart Association (AHA) along with American Stroke Association (ASA), in their 2015 guidelines for the management of spontaneous intracerebral hemorrhage, recommends the following:
 - For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (class I; level of evidence A) and can be effective for improving functional outcome (class IIa; level of evidence B)
 - For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous IV infusion and frequent BP monitoring (class IIb; level of evidence C)
 - Once the acute phase is over, BP should be controlled in all ICH patients (class I; level of evidence A). Measures to control BP should begin immediately

after ICH onset (class I; level of evidence A). A long-term goal of BP <130 mmHg systolic and 80 mmHg diastolic is reasonable (class IIa; level of evidence B).

The European Stroke Organization's recommendations are similar:

- In acute ICH within 6 hours of onset, intensive BP reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.
- Lowering of BP for secondary prevention after ICH is strongly recommended.
- For acute ischemic stroke: The AHA/ASA guideline for acute ischemic stroke of 2013 recommends:
 - In patients with markedly elevated BP who do not receive fibrinolysis, a reasonable goal is to lower BP by 15% during the first 24 hours after onset of stroke. The level of BP that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the SBP is >220 mmHg or the DBP is >120 mmHg (class I; level of evidence C).
 - For patients who are candidates for fibrinolysis, BP is <185/110 mmHg. Labetalol is recommended 10–20 mg intravenously over 1–2 minutes. It may be repeated one time; or nicardipine 5 mg/h intravenous, which may be titrated up by 2.5 mg/h every 5–15 minutes up to a maximum dose of 15 mg/h. When the desired BP is reached, the dose must be adjusted to maintain proper BP limits; or other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate. If BP is not maintained at or below 185/110 mmHg, recombinant tPA (rtPA) cannot be administered. After rtPA or other acute

reperfusion therapy is administered, BP has to be maintained at or below 180/105 mmHg. Blood pressure has to be monitored every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours. If BP is not controlled or DBP is >140 mmHg, IV sodium nitroprusside may be considered.²²

The European Stroke Organization's recommendations are:

- Routine BP lowering is not recommended following acute ischemic stroke
- Cautious BP lowering is recommended in patients with extremely high BPs (>220/120 mmHg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy
- It is recommended that abrupt BP lowering be avoided
- It is recommended that low BP secondary to hypovolemia or associated with neurological deterioration in acute stroke should be treated with volume expanders.

COMMON DRUGS WHICH ARE USED IN ACUTE STROKE (TABLE 1)

Although individual trials have shown some drugs ensure favorable outcome over others, there is no definite recommendation at present of choosing any particular agent. In acute phase, intravenous agents may be preferable for faster action and better control. Two trials studied the effect of continuation of pre-stroke medication versus discontinuation (ENOS, COSSACS).¹⁸ The outcome was better with discontinuation.

TABLE 1 Common drugs used for management of blood pressure in acute stroke

Drug	Dose	Mechanism of action	Onset of action	Half life	Side effects	Indications
Labetalol	15–20 mg bolus/15 mins max: 300 mg/day	Adrenergic blocker	5–10 min	3–6 h	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserina (if BP is reduced too rapidly),	Should be avoided in patients with asthma and acute left ventricular failure
Hydralazine	5–20 mg bolus every 15 min	Direct relaxation of arteriolar smooth muscle	10–20 min	1–4 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Nitroprusside	0.2–0.4 mg/h up to 0.8 mg/h	Releases nitric oxide	1–2 min	3–5 min	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserina (if BP is reduced too rapidly), thiocyanate, and cyanide toxicity	Should be used cautiously in patients with high intracranial pressure or azotemia.
Nitroglycerine	5–200 µg/min	Releases Nitric Oxide	3–5 min	1–2 min	Headache, tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, palpitations, methemoglobinemia, tolerance with prolonged use	Myocardial ischemia, heart failure

Contd...

Contd...

Drug	Dose	Mechanism of action	Onset of action	Half life	Side effects	Indications
Nicardipine	5–15 mg/h	Calcium channel blocker.	5–10 min	0.5–4 h	Tachycardia, headache, flushing, local phlebitis	Should be used cautiously in patients with myocardial ischemic or acute heart failure
Esmolol	250 g/kg bolus followed by 25–300 g/kg/min	Beta adrenergic blocker	5 min	9 min	Hypotension, nausea	Post operative after aortic dissection repair.
Enalaprilate	1.25–5 mg every 6 h	Angiotensin-converting enzyme inhibitor	15 min	1–4 h	Precipitous fall in BP in high-renin states, variable response	Should be avoided in acute MI and acute left ventricular failure

BP, blood pressure.

CONCLUSION

Blood pressure is often high during the acute period of both ischemic stroke and intracerebral hemorrhage. The effect of high BP on the outcome (both mortality as well as functional) of stroke is potentially adverse, although the evidence is still not clear. The evidence for the beneficial effects of treating BP in the acute phase of stroke is still inadequate and at times, contradictory. The treatment in that case is very cautious and only needed for very high BP in the acute ischemic strokes. The treatment needs to be more aggressive if the patient undergoes thrombolysis, or has any other comorbidity like ischemic heart disease, heart failure, and aortic dissection. For patients with ICH, the target SBP is lower. The benefits of BP lowering is only in the very acute phase of stroke (maximum benefit is first 6 hours). Blood pressure lowering in first 24 hours should not be more than 20% in case of ischemic stroke. After the first few days, the goal of antihypertensive therapy is prevention of recurrent strokes, and the target BP becomes much lower. If the patient was on any antihypertensive medications prior to the stroke, it is better to discontinue them in the acute phase and start medications suitable for the acute phase. In acute phase, intravenous agents are preferred for faster action and better control. Although some individual trials have pointed towards benefits of using some agents over others, presently there is no specific recommendation of choosing some specific drugs.

REFERENCES

- Leonardi-Bee J, Bath PMW, et al. IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315-20.
- Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med*. 2010;38:637-48.
- Donnelly J, Budohoski KP, et al. Regulation of the cerebral circulation: bedside assessment and clinical implications. *Critical Care*. 2016;20:129.
- Aiyagari V, Gorelick PB. Management of Blood Pressure for Acute and Recurrent Stroke. *Stroke*. 2009;40:2251-6.
- Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*. 2008;118:176-87.
- Feldstein CA. Early treatment of hypertension in acute ischemic and intracerebral hemorrhagic stroke: Progress achieved, challenges, and perspectives. *J Am Soc Hypertens*. 2014;8(3):192-202.
- Sakamoto Y, Koga M, Yamagami H, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *Stroke*. 2013;44:1846-51.
- AlSibai A, Qureshi AI. Management of Acute Hypertensive Response in Patients with Ischemic Stroke. *The Neurohospitalist*. 2016;6:122-9.
- Geeganage CM, Bath PM. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke. A meta-regression. *Hypertension*. 2009;54:775-81.
- Wahlgren NG, MacMahon DG, et al. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis*. 1994;4:204-10.
- Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377(9767):741-50.
- Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48-56.
- He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA*. 2014;311:479-89.
- Lee M, Ovbiagele B, Hong KS, et al. Effect of Blood Pressure Lowering in Early Ischemic Stroke Meta-Analysis. *Stroke*. 2015;46:1883-9.
- Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2014;(10):CD000039.
- IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RJ, Dennis M, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. *Lancet*. 2012;379:2352-63.
- Berge E, Cohen G, Lindley RJ, et al. Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the third international stroke trial of thrombolytic treatment for acute ischemic stroke. *Stroke*. 2015;46:3362-9.
- Woodhouse L, Scutt P, Krishnan K, et al. Effect of Hyperacute Administration (Within 6 Hours) of Transdermal Glyceryl Trinitrate, a Nitric Oxide Donor, on Outcome After Stroke: Subgroup Analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) Trial. *Stroke*. 2015;46:3194-201.
- Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation. Guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014 Oct;9:840-55.
- European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457-507.
- Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032-60.
- Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46:3020-35.

Use of Newer Antiepileptics in Status Epilepticus

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INTRODUCTION

There are four stages of status epilepticus (SE) (i) early, (ii) established, (iii) refractory, and (iv) super-refractory. While the early SE is invariably treated with benzodiazepines the treatment after benzodiazepines failure (established, refractory and super-refractory SE) is poorly understood. As of today, there is no robust data to support recommendations of any newer antiepileptics over another. In this article, some of the commonly used newer antiepileptics in the various situations of SE would be discussed in a concise manner. About 13 drugs find their place under the terms newer antiepileptic drugs; some of them are oxcarbazepine, vigabatrin, topiramate, zonisamide, levetiracetam, lacosamide, rufinamide, stiripentol, retigabine, eslicarbazepine, brivaracetam, ganaxolone, and perampanel. However, only levetiracetam and lacosamide have been tested for the spectrum of SE.

DEFINITION: STATUS EPILEPTICUS

Status epilepticus has been redefined as prolonged seizures after time point t_1 , which is 5 minutes from seizure onset and time point t_2 , which is 30 minutes after seizure onset that can have long-term consequence. The same holds true for 10 minutes and 60 minutes for focal SE with impaired consciousness, and 10–15 minutes and unknown for absence SE¹ (Table 1). The term established status epilepticus (ESE) is used for recurrent convulsions persisting after the use of benzodiazepines. The term refractory status epilepticus (RSE) is used when the status does not respond to both the first-line (usually benzodiazepines) and second-line antiepileptic.

Refractory SE occurs when SE fails to abort after a first-line (usually a benzodiazepine) and a second-line antiseizure medication have been given. It should be noted that time is not part of these definitions and are based only the medications given and persistence of seizures.

TABLE 1 International League against Epilepsy definitions of status epilepticus

	Time after which if seizures do not terminate patient is considered in status epilepticus (t_1)	Time after which on going seizures have long-term consequences (t_2)
Convulsive status epilepticus	5 min	30 min
Focal status epilepticus with impaired consciousness	10 min	60 min
Absence status epilepticus	10–15 min	Unknown
Other definitions of status epilepticus		
Established status epilepticus	Status epilepticus that persists after treatment with a benzodiazepine (1 st line treatment)	
Refractory status epilepticus	Status epilepticus that persists after a 1 st line agent (benzodiazepine) and 2 nd lines agent (additional agent such as levetiracetam, phenytoin, valproc acid) have failed	

LEVETIRACETAM

It is known that levetiracetam, a pyrrolidone derivative and piracetam analog, binds to synaptic vesicle protein 2A, but the precise mechanism of action is not clear.² It is recommended to give levetiracetam 2.5 g over 5 minutes or 1–4 g intravenously over 15 minutes. A maximum of 4.5 g can be given. Levetiracetam has the advantage of not causing many adverse reactions and also not interacting with other medications. It does accumulate in patients with renal dysfunction, however, the maintenance doses must be reduced in this setting.^{3,4}

- In a retrospective study, it was found that levetiracetam control ESE in 16 out of 18 patients (2008)⁵
- In another retrospective comparative study of levetiracetam, valproic acid, and phenytoin, the failure rate to abort ESE was 48.3%, 25.4%, and 41.4%, respectively (2011)⁶
- In a meta-analysis of eight studies, levetiracetam had the efficacy to the tune of 68.5% (2014)⁷
- Zheng et al. found levetiracetam as effective as valproic acid and other antiseizure drugs in the data that currently exist for ESE⁸ (2015).

LACOSAMIDE

Lacosamide came to the market in 2008, but its use for ESE began since 2009 when the intravenous form was made available. The mode of action is selective enhancement of the slow inactivation of voltage-gated sodium channels.² The most commonly used bolus dose is 400 mg intravenous, followed by a daily dose of 200–400 mg given in divided doses. The studies pertaining to lacosamide in SE are enumerated below:

- Nineteen studies (10 single-case reports and 9 case-series) with a total of 136 patients showed an overall success of aborting status of 56% and the most common side effects were mild sedation and hypotension.^{9,10} However, in these studies, Yasiry and Shorvon found only four patients qualifying as receiving lacosamide for ESE and concluded that this is an insufficient data⁷ (2013, 2014, and 2015)
- A randomized trial of lacosamide and fosphenytoin (TRENds) for nonconvulsive SE was stopped prematurely due to difficulty in recruiting patients. The result of this study may elucidate where lacosamide fits into treatment for the spectrum of SE¹¹ (2015).

FUTURE DIRECTIONS

At present, there are no direct comparisons of various antiepileptics for treating status once benzodiazepines have not worked. There is presently a study undergoing, the Established

Status Epilepticus Treatment Trial (ESETT), to compare the efficacy of fosphenytoin, levetiracetam, and valproic acid. A similar study in pediatrics, the Emergency Treatment with Levetiracetam or Phenytoin in status epilepticus in Children (EcLiPSE) trial, is currently going on. Until then, the studies discussed above provide the best evidence for management of ESE. Some workers have suggested use of phenobarbital or lacosamide as a second-line agent after benzodiazepines though the ongoing studies will not address the efficacy of phenobarbital or lacosamide.

The vast majority of the patients included in the studies discussed above excluded nonconvulsive status epilepticus (NCSE). The percentage of individuals with NCSE in intensive care units is estimated to be up to 20%, but there is little data about the best treatment for these individuals.

CONCLUSION

Presently, use of valproic acid, levetiracetam, phenobarbital or phenytoin has been suggested for use in ESE. Among these valproic acid seems to have an edge over others. There is not much data on the use of lacosamide. The treatment needs to be individualized though taking into consideration side effects of the drug and lack of clear superiority data of the various antiepileptics. There is need for prospective controlled randomized trials for ESE.

REFERENCES

1. Trinka E, Cock H, Rossetti A, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56:1515–23.
2. Wasim M, Husain A. Non-convulsive Seizure Control in the Intensive Care Unit. *Curr Treat Options Neurol*. 2015;17:1–9.
3. Brophy GM, Bell R, Classen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17:3–23.
4. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16:48–61.
5. Knake S, Gruener J, Hattermer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J Neurol Neurosurg Psychiatry*. 2008;79:588–9.
6. Alvarez V, Januel JM, Burnand B, et al. Second-line status epilepticus treatment: Comparison of phenytoin, valproate and levetiracetam. *Epilepsia*. 2011;52:1292–6.
7. Yasiry Z, Shorvon S. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies. *Seizure*. 2014;23:167–74.
8. Zheng F, Du C, Wang X. Levetiracetam for the treatment of status epilepticus. *Expert Rev Neurother*. 2015;15:1113–21.
9. Trinka E, Höfler J, Leitinger M, et al. Pharmacotherapy for Status Epilepticus. *Drugs*. 2015;75:1499–521.
10. Höfler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. *Epilepsia*. 2013;54:393–404.
11. Husain A. Lacosamide in status epilepticus: Update on the TRENds study. *Epilepsy Behav*. 2015;49:337–9.

Mechanical Devices and Pharmacological Thrombolysis in Stroke

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INTRODUCTION

Acute ischemic stroke is a very important cause of disability and death. Stroke incidentally is also the third leading cause of death globally. Ischemic strokes represent 80% of the total strokes and hemorrhagic strokes make up for the rest. Improved treatment is, therefore, needed to manage this devastating illness. "Time is brain" and urgent reperfusion of ischemic brain is the main objective of stroke treatment. Timely restoration of blood flow in stroke patients significantly reduces long-term morbidity. A successful recanalization increases the chances of favorable outcome by four times and reduces mortality rate by fourfolds.¹

The importance of recanalization is even more pronounced in basilar artery occlusion where the chances of leading an independent life are only 2% in patients without recanalization.² Last 2 decades have seen rapid advancement in the medical and endovascular management of acute ischemic stroke. Intravenous tissue-type plasminogen activator (tPA) was first to be introduced as a safe and effective thrombolytic agent followed by the newer thrombolytic agents, proposed as potentially safer drugs with more favorable interaction profiles. Rapid administration of Intravenous recombinant tPA (rtPA) to appropriate patients still remains mainstay of early stroke treatment.³

In addition to chemothrombolysis, other techniques including transcranial sonothrombolysis and microbubble cavitation have also been introduced. These developments in the medical therapies are paralleled with gradual but steady developments in endovascular recanalization techniques, which were initiated by the introduction of MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and Penumbra System. The introduction of Solitaire device was significant achievement in reliable and safe endovascular recanalization and was followed by further innovative devices—the Stent Retrievers.

The American Heart Association/American Stroke Association (AHA/ASA) has updated its guidelines on

endovascular treatment in acute ischemic stroke. These guidelines are based on outcome of five new clinical trials, viz., MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT.

The total number of ischemic stroke patients amenable to some form of endovascular revascularization intervention is probably a small subset of the total number. This disparity in part explains the slowness in the relatively slow progress in the stroke trial enrollment and scientific progress compared with more rapid developments in cardiac interventions. The number of acute stroke patients potentially requiring emergent intervention ranges only from 7 to 15% of the total number because the rest may have intracerebral hemorrhage (ICH), small vessel occlusion (lacunar infarct), transient ischemic attack (TIA), end-of-life strokes, or mild strokes that do not warrant the risk of endovascular procedure.⁴ Even in the communities with highly organized stroke programs only <10% stroke victims receive immediate treatment.

STROKE IMAGING

Neuroradiology has rapidly evolved over the last 2 decades. Acutely injured but salvageable brain tissue is not clinically discernable from the irrevocably infarcted tissue by mere physical examination. Most of the stroke patients will present with some core infarct that cannot be restored even by the most rapid intervention. However, many a times there may be a brain tissue with impaired blood flow surrounding the core infarct that may be saved by early intervention. This so called "ischemic penumbra" will progress to nonrecoverable infarct without rapid recanalization. In contrast, an infarct without penumbra will not improve with intervention and patients may actually be harmed with revascularization causing hemorrhagic transformation. Modern imaging may provide perfect information to draw this important distinction and to guide emergency team to take judicious decisions.

All the major stroke trials have relied on sensitivity and availability of nonenhanced computed tomography (CT)

brain scan for the presence or absence of brain stroke to determine patient enrollment. Ease of access, rapid scan time, and broad availability means that CT is the most commonly used form of acute stroke imaging and has the highest level of evidence. Therefore, nonenhanced CT brain scan remains the only cerebral imaging test required before IV-rtPA.

Magnetic resonance imaging (MRI) has specific advantages and disadvantages compared with CT. Diffusion-weighted images have proven to be both sensitive and specific to the presence of early cerebral ischemia. Magnetic resonance imaging can also be as sensitive to diagnose the presence of early hemorrhages as CT scan and hence also be used as a primary modality of imaging. However, MRI has too many disadvantages—limited availability, longer scan times and incompatibility of the magnetic environment with the iron-containing medical equipment, and conductive bioprosthesis.

The presence of core infarct can be determined by various modalities such as noncontrast cranial CT, collateral scores on CT angiography, CT perfusion scans, and MRI. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is used to quantify the amount of early ischemic changes in middle cerebral artery (MCA) territory present on noncontrast head CT. The ASPECT score is 10 points validated scoring system where an initial score of 10 indicates a normal CT scan and 1 point is subtracted for each abnormal area within 10 prespecified regions of the cortex and deep-cortical structures. The higher the number, the smaller the core infarct, the larger the presumed ischemic penumbra and better the patient as a candidate for intervention. Most of the endovascular trials have used a cut off of 6 as these patients are considered to have the largest areas of salvageable brain tissue.

INTRAVENOUS AND INTRA-ARTERIAL FIBRINOLYSIS

Intravenous fibrinolysis with rtPA remains the only Food and Drug Administration (FDA) approved treatment (level of evidence 1, class A recommendation) for stroke patients presenting within 3 hours after onset based on the National Institute of Neurological Disorders and Stroke rtPA Stroke Study (NINDS rtPA).

The European Study-Safe Implementation of Thrombolysis in the Stroke Monitoring Study (SITS-MOST) registry enrolling 6,483 patients confirmed the safety and efficiency of intravenous fibrinolysis. The European Cooperative Acute Stroke Study-III (ECASS-III) has now extended the time window and shown safety and efficacy of intravenous thrombolysis (IVT) with alteplase for acute ischemic stroke in selected patients treated 3–4.5 hours after stroke onset. Moreover, the latest AHA/ASA guidelines state that availability of endovascular treatment services should not supersede the use of IVT when indicated.

One of the main limitations of IV-rtPA since its approval has been strict 3-hour time window for initiating treatment (which was subsequently extended to 4.5 hours after ECASS-III). It has been found out that the complete or partial recanalization rates with IVT range between 39% and 65% and overall found to be lower than the one achieved by intra-arterial thrombolysis (IAT), which has recanalization rates between 72 and 88%. The differences in recanalization were most apparent in large-vessel occlusions [MCA and internal carotid artery (ICA)]. However, the recanalization rates for IVT are different for proximal and distal lesions also. Furthermore, in almost 33% cases, early reocclusion occurs after initial recanalization. Hence, endovascular procedures now a day are often seen to combine pharmacologic thrombolysis and mechanical clot manipulation under vision.⁵

Intra-arterial thrombolysis was first studied as an alternative to IV-rtPA to extend the window of thrombolysis beyond 4.5 hours. The IAT for acute stroke was first described by Zeumer in 1983.⁶ The idea behind IAT is rapid local delivery of thrombolytic agent through a microcatheter placed near the site of occlusion and infused over 1–2 hours. However, IAT has its own disadvantages also. The major disadvantage of IAT includes relative complexity of the procedure; technical expertise, selective availability; delays in initiating treatment and additional risk, and expense of an invasive procedure compared with IVT.⁷ The thrombolytics that can be used for IAT in acute stroke include—urokinase, prourokinase, streptokinase, alteplase, and reteplase.⁸ In general, the nonfibrin drugs (urokinase and streptokinase) can result in systemic hypofibrinogenemia whereas the fibrin selective agents (alteplase and recombinant prourokinase) are theoretically mostly active at the site of thrombosis.

The currently accepted indications for IAT include:

- Large stroke outside 4.5 hours window
- Improvement in National Institute of Health Stroke Scale (NIHSS) score or with further worsening of NIHSS score despite IVT
- Those who are ineligible for intravenous thrombolysis therapy.

The intravenously administered tPA and local IAT have both shown to improve the outcome. However, the time window for treatment and recanalization rates of both the approaches are limited.⁹ To improve the speed and frequency of recanalization combination of IVT and IAT is also done. This approach utilizes the advantages of IVT (fast and easy) and of IAT (directed therapy, titrated dosing, and higher rates of recanalization). The first of such trials was Emergency Management of Stroke (EMS) bridging trial. The outcome was that patients receiving combination of IV/intra-arterial rtPA had significantly more number of recanalization than the placebo (55–10%) whereas complications rates were similar.

Intravenous rtPA more or less remains the most important method of therapy for patients with large vessel occlusion, but still there are lots of limitations for IV-rtPA.

First, there is a very narrow-time window where in IV-rtPA is safe and effective. Second, treatment with IV-rtPA results in poorer rates of revascularization than endovascular therapy for proximal artery occlusions. Intravenous-rtPA recanalizes only one-third of proximal arterial occlusion including those of the ICA or MCA, on the other hand, IAT are designed to treatment of patients with proximal intracranial occlusion. Lastly, most of the patients are not eligible for IVT due to various contraindications like bleeding diathesis, recent surgery, or recent systemic events. Apart from rtPA, there are other additional acute reperfusion therapies that are also currently being investigated, which include tenecteplase and sonothrombolysis. The usual dose of IV-rtPA is 0.9 mg/kg to maximum of 90 mg. First 10% of the calculated dose is given as intravenous bolus dose. Remaining 90% of the calculated dose is given as infusion over 1 hour. If the patient's condition worsens and neurologic status is declining during tPA infusion then the following steps should be followed:

- Stop the infusion immediately
- Urgent call for neurologist
- Send blood sample for partial thromboplastin time; D-Dimer and fibrinogen
- Prepare for emergency CT.

MECHANICAL THROMBOLYSIS

Despite the clinical benefits of IV-rtPA, disappointments remained concerning modest recanalization rates, ranging between 4.4% for distal ICA occlusion, 4% for basilar artery occlusions, and 30% for MCA M1 and M2 segment occlusions.¹⁰ The importance of vascular recanalization in relation to outcome in acute ischemic stroke is very well established. This was instrumental in driving the research efforts to develop new endovascular devices to increase recanalization rates. This was provisionally shown in the MERCI trial, which achieved 46–48% rates of revascularization in arterial occlusion resistant to IV-rtPA.¹¹ Mechanical treatments include the use of catheters to directly deliver (during angiography) a clot-disrupting or retrieval device to a thromboembolus that is occluding a cerebral artery. Most devices are used in cerebral vessels that are 2–5 mm. Mechanical thrombolytic devices can remove a clot rapidly, whereas pharmaceutical thrombolytics, even those delivered intra-arterially, may take as long as 2 hours to dissolve a thrombus. The most recently developed devices, known as retrievable stents or stentriever, have shown higher recanalization rates and better outcomes than those seen with the older MERCI retriever.

The various techniques and approaches used for mechanical thrombolysis are:

- Thrombus disruption
- Immediate flow restoration with self-expandable stents (SESs)
- Thrombectomy.

Thrombus Disruption

In the landmark trial called prourokinase for acute cerebral thromboembolism (PROACT-II), the IAT consisted of local application of fibrinolytic drug at the proximal surface of the thrombus. Mechanical clot disruption in this process of fragmentation was not advocated. In thrombus disruption, the most common method is probing the thrombus with a microwire and then advancing the microcatheter into or beyond the thrombus. This simple procedure has been shown to improve the outcome. With the thrombus disruption in MCA territory, successful recanalization is reported in 79% as compared to 66% in PROACT-II.⁹

The endovascular photoacoustic recanalization system uses laser-based technology for clot disruption and it aims to emulsify the clot by the application of microcavitation bubbles at the tip of microcatheter. However, the mortality rate was significantly high in this technique.¹²

Stenting

Stent placement promises immediate flow restoration without repetitive passing and retrieval attempts. Instead of mechanical retrieval, intracranial stenting achieves recanalization by compressing the thrombus to the vessel wall and avoids the risk of proximal thrombus dislocation. However, the compressed thrombus can cause permanent side branch and perforator branch occlusions. Furthermore, the implant can have acute thrombosis requiring additional antiplatelet medication.¹³

Up to 32% restenosis rate is reported for bare metal intracranial stents in a 9 month follow-up. Self-expandable stents are preferentially used over balloon-mounted stents. Although the recanalization rates in all the studies on the application of SES in patients with stroke is generally very high, it is debatable whether stenting in an acute ischemic stroke has a future as a first-line treatment due to the risk involved in the intracranial stent placement and also due to the success of thrombectomy. Stenting, however, has clearly shown a great value in selected cases of rescue therapy. Of the 5 stent retriever trials, MR CLEAN, ESCAPE, and SWIFT PRIME permitted use of salvage intra-arterial fibrinolytic drugs whereas EXTEND-IA and REVASCAT did not. These data do not establish the benefit of intra-arterial fibrinolytic salvage nor could they establish lack of benefit. Such salvage techniques may be reasonable to employ in some special clinical circumstances.

Stent Retrievers

The most recently introduced mechanical devices for acute stroke treatment are SES like thrombectomy devices. They combine the advantages of temporary stenting with immediate flow restoration without the need for permanent

implantation plus thrombectomy resulting in a definitive thrombus removal. The stent retrievers offer a promising new treatment option for acute ischemic stroke. The first dedicated combined flow restoration and thrombectomy device for acute ischemic stroke was Solitaire flow restoration.

The various thrombolytic devices that are available include:

- Stryker neurovascular Trevo stent retriever
- Covidien Solitaire stent retriever system
- Concentric MERCI retriever system
- Penumbra system
- Snare-like devices
- Ekos ultrasound devices.

Mechanical Thrombectomy

Mechanical thrombectomy is successfully achieved by advanced and modified devices. All the devices are delivered by the endovascular access proximal to the occlusion site. The devices are divided into three groups according to where they apply force on thrombus.

Proximal Devices

They apply force to the proximal base of the thrombus. This group includes various aspiration catheters and systems.

Thrombus Aspiration and Proximal Thrombectomy

The first reports on mechanical thrombectomy in acute ischemic stroke treatment included use of aspiration catheters.¹⁴ A large microcatheter (4–5 Fr) is advanced to the proximal surface of the clot and suction force is applied using a 60 mL syringe. Entrapment of thrombus is indicated by the absence of backflow. The catheter is then retrieved with constant negative pressure to avoid the loss of thrombus. This method is technically simple, fast to apply, and relatively inexpensive. It is widely used in proximal occlusion (cervical ICA and ICA terminus) where the target vessel has a large diameter and got an anatomy that is favorable for device navigation.

Penumbra System

This is a refinement of proximal thrombectomy technique. It applies continuous aspiration pressure in conjunction with mechanical fragmentation. This was approved by FDA for clot removal in stroke treatment in 2007.

Distal Devices

They approach the thrombus proximally but then are advanced by a microcatheter past the thrombus to be unsheathed behind it. In these devices, flow force is applied to the distal base of thrombus. This group includes brush-like, basket-like and coil-like devices.

Distal Thrombectomy

There is a technical disadvantage associated with large diameter aspiration catheters. Hence a novel generation of distal thrombectomy device was developed. In this procedure after passing the clot, the device is deployed distal to the thrombus. However, as expected, vasospasm and vessel wall damage have been more frequently described in association with distal devices. Furthermore, during retrieval, the loss of engagement of clot with the distal device is more prone to cause thromboembolic events. Hence, for most of the distal devices a proximal balloon occlusion and aspiration port from guiding catheter during retrieval is recommended.

Stent-like Device

The most recently developed devices include stent-like devices that are placed across the occlusion site, deployed within the thrombus and then retrieved. This group includes various SES retrievers.

TREATMENT RECOMMENDATIONS

- Mechanical thrombectomy as an adjunct to IVT within 4.5 hours if no contraindication in acute ischemic stroke due to occlusion of a large artery in anterior circulation. All efforts should be made not to delay IVT if indicated while organizing for mechanical thrombectomy or vice-versa. Both of these procedures should be done on an emergency basis with least delay
- Other clot retrieving or aspiration device may be used in centers with experience in order to achieve maximum patency of the target vessel
- In conditions, where IVT is contraindicated (e.g., warfarin-treated with therapeutic international normalized ratio) initial treatment with mechanical thrombectomy may be tried
- In specialized centers, in patients with acute basilar artery occlusion, multidisciplinary team (neurointensivist/neuroanesthesiologist/stroke physician) need to make a decision based on multimodality imaging about combining IVT with mechanical thrombectomy. Role of neurointerventionist and choice of anesthesia is very important and should be individualized without causing undue delay in thrombectomy.

Patient Selection

- Intracranial vessel occlusion must be diagnosed with noninvasive imaging before considering treatment with mechanical thrombectomy
- If vessel imaging is not available at baseline, a NIHSS score of 9 within 3 hours, and 7 points within 6 hours may indicate the presence of large-vessel occlusion

- Patients with radiological signs of large infarcts (for example using the ASPECTS score) may be unsuitable for thrombectomy
- Imaging techniques for determining infarct and penumbra sizes can be used for patient selection and correlate with functional outcome after mechanical thrombectomy
- High age alone is not a reason to withhold mechanical thrombectomy as an adjunctive treatment.

ANESTHESIA IN MECHANICAL THROMBECTOMY

Conscious sedation has gained support from a retrospective analysis of patients receiving either general anesthesia or conscious sedation. Patients receiving general anesthesia had significantly more in-hospital mortality (25%) and pneumonia (17%) compared to patients receiving conscious sedation (12% and 9.3%, OR 2.37 and 2.0, respectively) but with similar rates of spontaneous ICH.¹⁵ An expert consensus statement of the Society of Neurointerventional Surgery and the Neurocritical Care Society recommends the use of general anesthesia only for patients with severe agitation, low level of consciousness (Glasgow Coma Scale <8), loss of airway protective reflexes, respiratory compromise, and in selected posterior circulation stroke presenting with these features.¹⁶

CONCLUSION

The introduction of mechanical recanalization techniques is the treatment of acute ischemic stroke has undoubtedly broadened the spectrum of patients for stroke. The time window is broadened to 8 hours after the onset of stroke. However, within the time window of 4.5 hours, the indication for mechanical thrombectomy in relation to IV-rtPA is a subject of debate and further research. Furthermore, in cases of proximal artery occlusion (carotid termination and ICA-MCA tandem occlusion) with high-thrombus burden, mechanical approaches are likely to succeed in future. To achieve successful mechanical thrombectomy various approaches and devices are advocated in recent years. However, the most frequently applied group of devices is stent retrievers. The role of stent retrievers within the early time window, the impact of bridging therapy, the percentage of complications like ICH; and periprocedural aspects like impact of general anesthesia on safety and clinical outcome are some of the additional aspects of endovascular stroke treatment that will require further attention in future. Nevertheless, the current endovascular stroke treatment remains a multimodal

approach combining the advantages of different mechanical thrombolysis techniques often in conjunction with IAT. The endovascular treatment, in particular thrombectomy as an add-on to intravenous rtPA, provides beneficial functional outcomes after ischemic stroke secondary to occlusion of anterior large vessels, without increased detrimental effects compared with medical care alone. Considering the severity of intracranial complications, the endovascular recanalization techniques should be reserved to dedicated stroke centers.

REFERENCES

1. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38:967-73.
2. Lindsberg PJ, Malth HP. Therapy of basilar artery occlusion; a systematic analysis comparing intra-arterial & intravenous thrombolysis. *Stroke*. 2006;37:922-8.
3. Jauch EC, Saver JL, Adams HP Jr, et al. On behalf of AHA stroke council. *Stroke*. 2013;44:870-947.
4. Cloft HJ, Rabinstein A, Lanzino G, et al. Intra-arterial stroke therapy. An assessment of demand and available work force. *AJNR Am Neuroradiol*. 2009;30:453-8.
5. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948-54.
6. Zeumer H, Hacke H, Ringelstein EB. Local intraarterial thrombolysis in vertebrobasilar thromboembolic disease. *AJNR Am Neuroradiol*. 1983;4:401-4.
7. Nogueira RG, Schwamm LH, Hirsch JA. Endovascular approaches to acute stroke, Part 1: Drugs, devices and data. *AJNR Am Neuroradiol*. 2009;30:649-61.
8. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol*. 1992;32:78-86.
9. Arnold M, Schroth G, Nedeltchev K, Lohr T, Remonda L, Stepper F, et al. Intra-arterial thrombolysis in 100 patients with acute stroke due to MCA occlusion. *Stroke*. 2002;33:1828-33.
10. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalisation with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke*. 2010;41:2254-8.
11. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36:1432-8.
12. Bertis A, Lutsep H. Mechanical thrombolysis in acute stroke with ischemic endovascular photoacoustic recanalisation. *Stroke*. 2004;35:1112-6.
13. Diener HC, Bougrovslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-7.
14. Chapot R, Floudart E, Rogopoulos A, et al. Thromboaspiration in the basilar artery report of 2 cases. *AJNR Am Neuroradiol*. 2002;23:282-4.
15. McDonald JS, Brinjikji W, Rabinstein AA, et al. Conscious sedation versus general anaesthesia during mechanical thrombectomy for stroke: a propensity score analysis. *J Neurointerv Surg*. 2015;7:789-94.
16. Talke PO, Sharma D, Heyer EJ, et al. Republished: Society for neuroscience in anesthesiology and critical care expert consensus statement: anaesthetic management of endovascular treatment for acute ischemic stroke. *Stroke*. 2014;45:138-50.

Cerebral Tissue Oxygen Saturation Monitoring in Cardiac Surgical Patients

Matthew J Chan, Rinaldo Bellomo

INTRODUCTION

Postoperative cognitive dysfunction (POCD) is common following cardiopulmonary bypass (CPB) in cardiac surgical patients.¹⁻³ Such POCD is likely triggered by cerebral oxygen desaturation,² secondary to cerebral hypoperfusion and microembolism.⁴⁻⁷ Thus, intraoperative cerebral oxygen desaturation is an important risk factor for POCD. As a result, regional cerebral tissue oxygen saturation (SctO₂) monitoring using near-infrared spectroscopy (NIRS) has become a promising area of investigation in the management of cardiac surgical patients. However, SctO₂ monitoring with NIRS has not yet become part of standard practice, both during and after CPB, and there is a need to review current knowledge gaps before widespread application becomes justified.

Near-infrared spectroscopy estimates SctO₂ non-invasively from the differential absorbance of light by oxygenated and total hemoglobin. Sensors for each brain hemisphere are placed on the forehead, using one receiver to capture light scattered primarily through frontal lobe cerebral tissues with one receiver and another to capture and subtract the signal from superficial vessels (Fig. 1).^{8,9} Near-infrared spectroscopy principally reflects venous oxygenation, given the proportionally greater volume of the venous system (~70-75%).¹⁰ Thus, NIRS provides potential estimates of the balance between bifrontal oxygen supply and demand. From such information, inferences can be made about global SctO₂, cerebral blood oxygenation, cerebral blood flow, and cerebral metabolic rate.¹¹ It is also important for monitoring to be performed on both left and right cerebral hemispheres, given the differing physiological state of each hemisphere in each patient and to differentiate any potential pathology present in a hemisphere.

Given its potential usefulness, a range of commercial NIRS devices is now available. Each device differs in its superficial signal subtraction algorithm and depth of tissue penetration. As such, the precision and accuracy of each available NIRS system are both known to vary greatly.¹² Importantly, NIRS

differs from pulse oximetry in that it does not gate its signal with the arterial pulse. It, therefore, has additional uses even when there is nonpulsatile cerebral blood flow, such as in continuous flow during CPB.¹¹ Additionally, NIRS may be favored over jugular venous bulb oximetry, previously the most comprehensive measure of cerebral oxygen physiology for cerebral physiological monitoring due to its noninvasive nature, ease of application of sensors and "continuous" recordings updated every few seconds. These advantages also extend to other fields, including cardiac arrest, where its ease of application and ability for use in pulseless patients allows for greater awareness of prognosis and success of resuscitative interventions.

However, limitations do exist in the use of NIRS for cerebral oximetry in cardiac surgery. True validation of NIRS readings to jugular venous bulb oximetry has been challenging and is rarely performed in healthy subjects



FIG. 1: Near-infrared spectroscopy INVOS™ system on a patient (deidentified)

Courtesy: Department of Intensive Care, Austin Health, Heidelberg, Victoria, Australia.

due to the evident ethical challenges in performing invasive procedures in such subjects.^{11,12} Furthermore, questions have been raised regarding the relationship between NIRS readings and skin pigmentation or gender, as well as interference from other molecules similar to hemoglobin.^{12,13} Finally, the cost of the device and the single-use sensors have been a barrier to the uptake of NIRS in the clinical setting outside of research.

Continuous NIRS monitoring of SctO₂ may, therefore, be useful in the detection of cerebral oxygen desaturation both intraoperatively and postoperatively. Cerebral tissue oxygen saturation is known to be affected by a number of measurable physiological variables with 85% of its variability accounted for by a combination of hemoglobin, temperature, pH, and partial arterial pressure of carbon dioxide (PaCO₂).¹⁴ To date, however, there remain gaps in clinical knowledge regarding both the use of NIRS technology and interventions shown to successfully optimize SctO₂ in cardiac surgical patients. In order to diagnose cerebral oxygen desaturation, it is crucial to define the normal baseline reference values for regional cerebral tissue oxygen saturation. However, there is a lack of information on what constitutes a normal SctO₂ in the cardiac surgical patient cohort, despite the value of such information in the management of cardiac surgical patients, both intraoperatively and postoperatively during recovery in the intensive care unit (ICU).

Accordingly, the authors systematically reviewed all randomized controlled trials (RCTs) aiming to identify the normal baseline range of SctO₂ values in cardiac surgical patients as estimated using NIRS, as well as the nature and efficacy of interventions seeking to modulate SctO₂. The authors also aimed to synthesize available information in included studies on postoperative SctO₂ and POCD.

NORMAL BASELINE CEREBRAL TISSUE OXYGEN SATURATION

An aggregated range for normal baseline SctO₂ in cardiac surgery patients has significant value in preoperative planning, perioperative risk estimation and assessment of whether a given intervention can restore SctO₂ to normal. Despite this, normal baseline SctO₂ values remain unclear. Using the Medline, Embase, and Central databases for RCTs of adult cardiac surgical patients in which baseline SctO₂ was measured and reported, the authors identified 11 RCTs fulfilling our inclusion and exclusion criteria. Table 1 shows the characteristics of these studies. Of note, these studies had widely varying patient cohorts and characteristics with two RCTs being performed in only high risk patients. All baseline preoperative SctO₂ data reported were recorded (Table 2) and used to calculate an overall pooled mean and standard deviation across all RCTs of 66.4% with a wide standard

TABLE 1 Characteristics of included studies

Study authors	Year	Number randomized	Country of study	NIRS machine used	Study population and comorbidities	Study primary findings
Brassard et al.	2014	31	Canada	INVOS* (Somanetics, Troy, MI, USA)	Any cardiac surgery: <ul style="list-style-type: none"> • 74% CAD • 42% VHD • 45% diabetes • 77% HTN 	Administration of norepinephrine to restore MAP during CPB in diabetic patients associated with reduction in cerebral oxygen saturation (not in patients w/o diabetes); administration of phenylephrine associated with trend toward greater reduction in diabetic patients
Guclu et al.	2014	80 (only 37 reported)	Turkey	INVOS 3100 (Somanetics, Troy, MI, USA)	CABG (elective) <ul style="list-style-type: none"> • 24% "other coexisting disease" 	Higher cerebral oxygen saturation in patients with sevoflurane anesthesia maintenance compared to total intravenous anesthesia
Kim et al.	2009	60	Korea	INVOS 5100 (Somanetics, Troy, MI, USA)	CABG w/o CPB <ul style="list-style-type: none"> • 38% diabetes • 63% HTN 	Single dose midazolam during induction of anesthesia preserves cerebral oxygen saturation to a similar degree to propofol
Kok et al.	2014	60 (1 exclusion)	Netherlands	INVOS 5100C (Somanetics, Troy, MI, USA)	CABG (all patients OK for CPB or no CPB) <ul style="list-style-type: none"> • 23% diabetes • 29% HTN 	Incidence of cerebral oxygen desaturation is uncommon in low-risk patients and not different between CPB and non-CPB patients
Lenkin et al.	2013	40	Russia	FORE-SIGHT* (CASMED, Branford, CT, USA)	Multiple valve repairs/replacements (high risk)	Normothermic CPB patients have higher cerebral oxygen saturation during combined valve surgery compared to hypothermic CPB

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Study authors	Year	Number randomized	Country of study	NIRS machine used	Study population and comorbidities	Study primary findings
Mohandas et al.	2013	100	India	EQUANOX 7600 (Nonin, Plymouth, MN; USA)	Any cardiac surgery w/o CPB	Intraoperative cerebral oxygen saturation monitoring decreases the incidence of postoperative cognitive decline
Murkin et al.	2007	200 (6 exclusions)	Canada	INVOS 5100 (Somanetics, Troy, MI, USA)	CABG w/o CPB (elective) • 28.5% diabetes • 17.5% COPD	Intraoperative cerebral oxygen saturation monitoring decreases the incidence of major organ morbidity and mortality
Negargar et al.	2007	72	Iran	INVOS 4100 (Somanetics, Troy, MI, USA)	Any cardiac surgery (elective) • 67% CABG • 33% valve surgery • 15% diabetes	Cerebral oxygen desaturation may help to predict neurological complications, although not statistically significant
Piquette et al.	2007	32 (2 exclusions)	Canada	INVOS 4100 (Somanetics, Troy, MI, USA)	Any cardiac surgery w/o CPB (elective, Parsonnet score >15—high risk) • 63% CABG • 80% valve surgery • 17% diabetes • 67% HTN	IV NTG infusion before/during CPB helps to maintain cerebral oxygen saturation during CPB in high-risk patients
Schoen et al.	2011	128 (18 exclusions)	Germany	INVOS 5100 (Somanetics, Troy, MI, USA)	Any cardiac surgery w/o CPB • 84% CABG • 37% valve surgery	Intraoperative cerebral oxygen desaturation associated with worse early cognitive outcomes; sevoflurane-based anesthesia may be associated with better postoperative cognitive function compared with propofol-based anesthesia
Vretzakis et al.	2013	150 (13 exclusions)	Greece	INVOS 5100 (Somanetics, Troy, MI, USA)	Any cardiac surgery w/o CPB (elective) • 89% CABG • 18% valve surgery • 55% previous MI • 24% diabetes • 81% HTN • 21% COPD	Cerebral oxygen saturation as part of a RBC transfusion protocol reduces use of RBC

*Model number not reported.

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; CAD, coronary artery disease; VHD, valvular heart disease; HTN, hypertension; MI, myocardial infarction; COPD, history of chronic obstructive pulmonary disease; MAP, mean arterial pressure; IV, intravenous; NTG, nitroglycerin; w/o, without.

deviation of close to 8%, a 95% confidence interval (CI) between 65.0 and 67.7%, and a 95% reference range between 51.0 and 81.8%. Unfortunately, considerable statistical heterogeneity was found among studies on analysis of the data, with a high I^2 statistic close to 90% (Fig. 2).

Additionally, the authors performed sensitivity analyses limiting the data to measurements of each cerebral hemisphere; removal of studies with varying NIRS machines; removal of studies with high risk of bias; and removal of studies of high risk patient groups, where there was a severity of disease inclusion criterion, such as surgery for complex cardiac disease or a high-presurgical risk score. These did

not demonstrate a significant difference on visual inspection of the data. In particular, pooled data on $SctO_2$ for the left hemisphere only and right hemisphere only were different at 65.4% and 64.7%, respectively, and the funnel plot of all studies and subgroups was asymmetrical.

The 95% reference range calculated from the spread of the pooled data was wide, suggesting that baseline $SctO_2$ values can vary greatly in this heterogeneous patient cohort.

This spread remained even after removal of studies including only high risk patients. Further detailed study is indicated to assess the patient characteristics associated with their baseline $SctO_2$, such as height/weight and comorbidities.

TABLE 2 Baseline preoperative cerebral tissue oxygen saturation: summary table, pooled analysis and sensitivity analysis

Study	Study arm/ interventions	Study subgroup	Hemisphere	Number of patients	Mean \pm SD	95% CI	Normal range quoted	Study referenced
Brassard 2014	Norepinephrine (to keep MAP >60 mmHg)	Diabetics	–	6	60 \pm 11	51.2–68.8	None stated	
		Non-diabetics	–	8	61 \pm 9	54.8–67.2		
	Phenylephrine (to keep MAP >60 mmHg)	Diabetics	–	8	63 \pm 3	60.9–65.1		
		Non-diabetics	–	9	65 \pm 6	61.1–68.9		
Guclu 2014	Sevoflurane (for anesthesia maintenance)		L	16	66.4 \pm 7.7	62.6–70.2	None stated	
			R	16	64.5 \pm 7.1	61.0–68.0		
	Total intravenous anesthesia		L	21	66.4 \pm 10	62.1–70.7		
			R	21	66.5 \pm 7.9	63.1–69.9		
Kim 2009	Midazolam (induction of anesthesia)		L	30	65 \pm 9	61.8–68.2	None stated	
			R	30	64 \pm 10	60.4–67.6		
	Propofol (induction of anesthesia)		L	30	66 \pm 7	63.5–68.5		
			R	30	66 \pm 7	63.5–68.5		
Kok 2014	Overall		–	59	67.1 \pm 9.4	64.7–69.5	None stated	
	With CPB		–	29	67.2 \pm 10.1	63.5–70.9		
	Without CPB		–	30	67 \pm 8.8	63.9–70.1		
Lenkin 2013	Normothermic CPB		–	20	65 \pm 8	61.5–68.5	65–75%	None referenced
	Hypothermic CPB		–	20	64 \pm 6	61.4–66.6		
Mohandas 2013*	Cerebral oxygenation monitoring		L	50	66.32*	–		
			R	50	65.78*	–		
	No monitoring		L	50	66.38*	–		
			R	50	65.42*	–		
Murkin 2007	Cerebral oxygenation monitoring		–	100	68.9 \pm 7.2	67.5–70.3	None stated	
	No monitoring		–	100	70.3 \pm 7.1	68.9–71.7		
Negargar 2007	CABG with CPB		–	24	77.3 \pm 8.3	74.0–80.6	55–75% (see introduction)	Paula et al. 2001 (incor- rect refer- ence)
	CABG without CPB		–	24	75.6 \pm 7.9	72.4–78.8		
	Valve surgery		–	24	70.8 \pm 9.6	67.0–74.6		
Piquette 2007	Glyceryl trinitrate		L	15	54 \pm 11	48.4–59.6	Not stated	
			R	15	51 \pm 8	47.0–55.0		
	Control		L	15	63 \pm 8	59.0–67.0		
			R	15	59 \pm 11	53.4–64.6		
Schoen 2007	Sevoflurane	No desaturations	–	42	66.2 \pm 6	64.4–68.0	Not stated	
		Desaturations	–	14	60.2 \pm 7.8	56.1–64.3		
	Propofol	No desaturations	–	34	66 \pm 4.6	64.5–67.5		
		Desaturations	–	20	57.6 \pm 8.6	53.8–61.4		

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Study	Study arm/ interventions	Study subgroup	Hemisphere	Number of patients	Mean \pm SD	95% CI	Normal range quoted	Study referenced
Vretzakis 2013	Cerebral oxygenation monitoring		L	75	66.29 \pm 7.48	64.6–68.0	Not stated	
			R	75	66.56 \pm 7.31	64.9–68.2		
		Inclusion groups	Number of patients/ readings	Pooled mean	SE of pooled mean	95% CI of pooled mean	SD of pooled mean	Reference ranges (2.5% quantile to 97.5% quantile)
	Pooled results	All*	814 (1,116 total readings)	66.4	0.65	65.0–67.7	7.84	51.0–81.8
	Sensitivity analyses	L only*	302	65.4	0.71	63.8–67.0	8.82	48.1–82.7
		R only*	302	64.7	0.98	62.4–66.9	8.65	47.7–81.7
		INVOS™ only	674 (876 readings)	66.5	0.81	64.9–68.2	7.88	51.1–81.9
		Non-INVOS™ only*	140 (240 readings)	65.7	0.27	65.0–66.4	13.78 [#]	38.7–92.7 [#]
		Low/unclear risk of bias only*	480 (670 readings)	66.0	0.94	64.1–68.0	8.26	49.8–82.2
		Non-high-risk patients only*	744 (1,016 readings)	67.0	0.58	65.8–68.2	7.76	51.8–82.2

Note:

- Means and standard deviations listed as reported.
- All values listed as percentage (%).
- Only means reported (no measure of variance).

*Mohandas 2013 included in mean and SE calculation but removed from SD/reference ranges/heterogeneity calculations (no SDs reported)

[#]Only Lenkin 2013 was used to calculate this.

L, left; R, right; –, unclear/bifrontal; SE, standard error; SD, standard deviation; CI, confidence interval; CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

This information would contribute to our knowledge of the relationships between patient factors, baseline SctO₂, and operative outcomes.

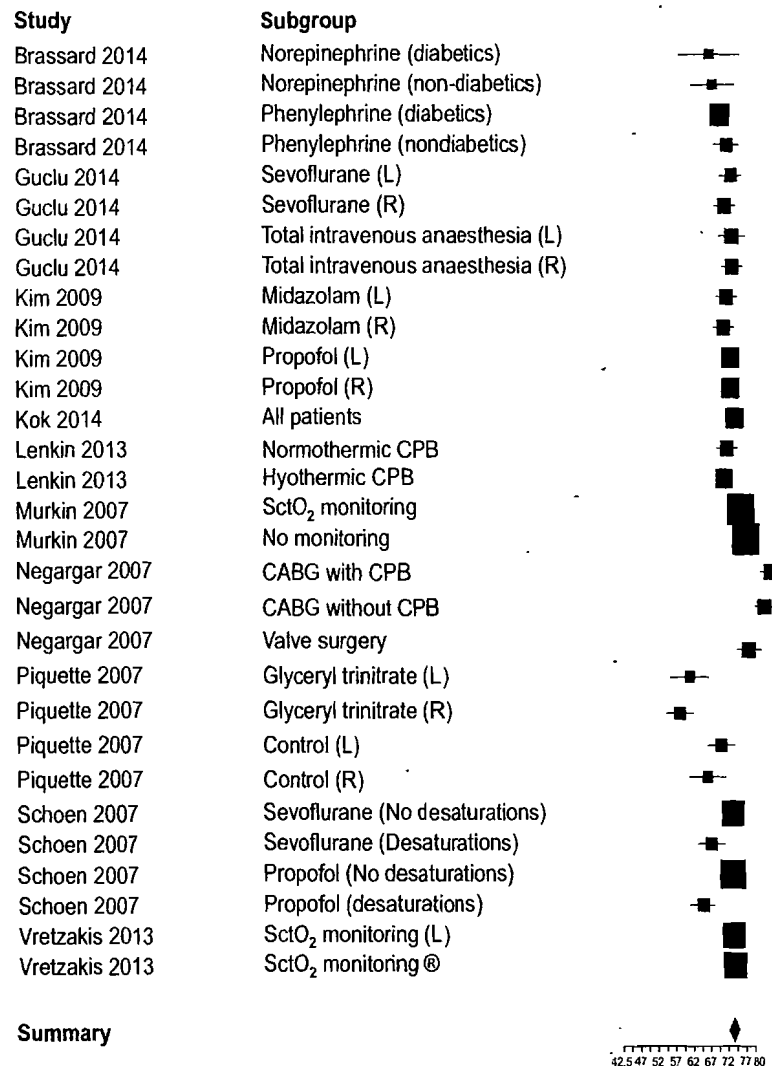
On risk of bias assessment using standardized Cochrane methods, methodological quality of studies in this area was variable with only one RCT satisfying a low risk of bias in all domains evaluated. This, in addition to the evident clinical and statistical heterogeneity of included studies, limits the generalizability of our findings and highlights the need for a more rigorous research approach in this field.

The authors also note that a wide variety of NIRS systems and models were used in these studies with the most popular being the INVOS™ system. As device precision and accuracy significantly differ from machine to machine, this adds some further methodological heterogeneity to the pooled data.

Our results correlate well with observational studies of SctO₂ in the cardiac surgical patient population. In the largest

prospective observational study of preoperative SctO₂ of 1,178 German adult cardiac surgery patients requiring CPB,¹⁵ investigators reported a median baseline SctO₂ on room air of 62% (57–67%) on the left and 62% (56–67%) on the right using the INVOS™ system. This study reported that preoperative SctO₂ levels correlated strongly with baseline cardiopulmonary function and were associated with poorer postoperative outcomes. This study highlights the importance of gaining a close understanding of preoperative SctO₂ in the context of the management of intraoperative desaturations with important implications particularly for surgical risk stratification.

Another prospective observational study of 101 cardiac surgery patients requiring CPB using the INVOS™ system found mean baseline SctO₂ values of 58.6%.³ These comparatively lower values may be explained by the smaller sample size as well as the study protocol, which involved collection of the lower SctO₂ value of the hemispheres for a single reading at each time point. As described previously,



CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; SctO₂, cerebral tissue oxygen saturation.

FIG. 2: Baseline cerebral tissue oxygen saturation: Forest plot of point estimates and confidence intervals of all studies and subgroups

this methodology fails to account for the differing physiology across the cerebral hemispheres, taking a singular value for SctO₂.

To the authors' knowledge, theirs is the first RCT-based comprehensive estimate of normal baseline values for SctO₂ in adult cardiac surgery patients from meta-analysis of the literature. This likely provides the most robust dataset for future comparisons and interventions. Of note, only two RCTs in the literature quoted a normal range for SctO₂: one¹⁶ with an unreferenced statement of 65–75%, and another¹⁷ with figures of 55–75% from a reference that did not actually contain such information.

While these figures are similar to our aggregated results, the vague sources are demonstrative of the uncertainty surrounding normal SctO₂ values, and limit the implications resulting from these studies. Comparisons between normal and abnormal are necessary to contextualize and validate

the findings as well as to find clinical application for SctO₂ readings.

INTRAOPERATIVE CEREBRAL TISSUE OXYGEN SATURATION AND THE EFFECT OF INTERVENTIONS

With a clearer understanding of what is normal in cerebral oximetry in cardiac surgery patients, it becomes easier to interpret studies assessing potential interventions to prevent or treat intraoperative cerebral oxygen desaturations. Such interventions, if found to be successful, would be invaluable in cardiac surgery management, potentially limiting the incidence of POCD in these patients.

In the 11 RCTs included in the above review, investigators studied eight interventions (Table 3):

TABLE 3 Summary table of effects of interventions on intraoperative cerebral tissue oxygen saturation, mortality and postoperative cognitive dysfunction

Intervention	Studies tested and reported	Time-points reported/ subgroups	Hemisphere	Number of participants (control vs. intervention)	Control mean difference (compared to baseline)	Intervention mean difference (compared to baseline)	Mean effect size and standard error	95% CI	p-value	Mortality (control vs. intervention)	POCD (control vs. intervention)/ measure of POCD
Cerebral oxygenation monitoring vs. no monitoring	Murkin 2007	Mean throughout surgery	-	100 vs. 100	-6.9 ± 1.0	-5.3 ± 1.0	1.6 ± 0.14	1.32–1.88	<0.001	1% vs. 0% (ITT analysis: p = 0.50)	-
	Mohandas 2013*									-	Test values directly compared*** (MMSE and ASEM)
	Vretzakis 2013*									1.3% vs. 1.3% (p = 1.0)	-
CABG with CPB vs. without CPB	Negargar 2007	1 st hour of surgery	-	24 vs. 24	-4.8 ± 2.3	-3.8 ± 2.6	1.0 ± 0.71	-0.43–2.43	0.165	-	4% vs. 4% (p = 1.0)
		2 nd hour of surgery			-6.5 ± 2.3	-5.6 ± 2.4	0.9 ± 0.68	-0.47–2.27	0.191		Measured with MMSE
		3 rd hour of surgery			-8.1 ± 2.3	-11.4 ± 2.8	-3.3 ± 0.74	-4.79–	<0.001		(decrease >20% and 1SD)
		4 th hour of surgery			-9.8 ± 2.5	-9.8 ± 1.7	0 ± 0.61	-1.81	1.000		62% vs. 53% (p = 0.5)
		5 th hour of surgery			-13.1 ± 2.2	-6.9 ± 3.1	6.2 ± 0.78	-1.24–1.24	<0.001		Measured with Cogstate battery (-2 change in Z-score in 2+ tasks)
								4.64–7.76			
	Kok 2014									-	
Normothermic CPB vs. hypothermic CPB**	Lenkin 2013	Start of CPB	-	20 vs. 20	-1.0 ± 1.8	1.0 ± 2.1	2.0 ± 0.62	0.75–3.25	0.003	-	-
		30 minutes into CPB			5.0 ± 1.8	6.0 ± 2.0	1.0 ± 0.61	-0.23–2.23	0.107		
		60 minutes into CPB			3.0 ± 2.3	6.0 ± 2.0	3.0 ± 0.68	1.26–4.74	0.001		
		90 minutes into CPB			3.0 ± 2.1	8.0 ± 2.0	5.0 ± 0.66	3.66–6.34	<0.001		
		120 minutes into CPB			0 ± 1.8	9.0 ± 2.2	9.0 ± 0.64	7.71–10.29	<0.001		
Glyceryltrinitrate during pre-CPB and CPB vs. placebo	Piquette 2007	Start of CPB	L	15 vs. 15	-2.0 ± 3.5	2.0 ± 4.4	4.0 ± 1.45	1.03–6.97	0.010	0% vs. 13% (p-value not provided)	-
			R		-3.0 ± 4.6	2.0 ± 3.5	5.0 ± 1.49	1.94–8.06	0.002		
		End of CPB	L		-11 ± 4.2	2.0 ± 3.4	13.0 ± 1.40	10.14–15.86	<0.001		
			R		-13 ± 4.6	2.0 ± 2.7	15.0 ± 1.38	12.18–17.82	<0.001		
Midazolam as part of induction of anesthesia vs. propofol	Kim 2009	5 min after administration	L	30 vs. 30	8.0 ± 1.9	9.0 ± 2.3	1.0 ± 0.55	-0.09–2.09	0.071	-	-
			R		8.0 ± 1.9	9.0 ± 2.5	1.0 ± 0.57	-0.15–2.15	0.086		

Contd...

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Intervention	Studies tested and reported	Time-points reported/ subgroups	Hemisphere	Number of participants (control vs. intervention)	Control mean difference (compared to baseline)	Intervention mean difference (compared to baseline)	Mean effect size and standard error	95% CI	p-value	Mortality (control vs. intervention)	POCD (control vs. intervention)/ measure of POCD
Sevoflurane anesthesia vs. total intravenous anesthesia	Guclu 2014	Intubation	L	16 vs. 16	4.3 ± 3.8	7.1 ± 3.2	2.8 ± 1.24	0.26–5.34	0.032	–	–
			R		5.2 ± 3.1	6.9 ± 2.6	1.7 ± 1.01	–0.37–3.77	0.103		
		Internal mammary artery dissection	L		–1.9 ± 3.5	–1.4 ± 3.1	0.5 ± 1.17	–1.89–2.89	0.672		
			R		–2.5 ± 2.8	–2.9 ± 2.6	–0.4 ± 0.96	–2.35–1.55	0.678		
		Cross-clamping	L		–10.6 ± 3.1	–1.8 ± 3.4	8.8 ± 1.15	6.45–11.15	<0.001		
			R		–7.6 ± 2.9	–4.7 ± 2.9	2.9 ± 1.03	0.81–4.99	0.008		
		Cooling to 34°C	L		–11.7 ± 3.5	–4.1 ± 3.5	7.6 ± 1.24	5.07–10.13	<0.001		
			R		–12.0 ± 3.5	–5.3 ± 2.6	6.7 ± 1.09	4.47–8.93	<0.001		
		At CPB lowest temperature	L		–17.8 ± 3.4	–4.0 ± 3.2	13.8 ± 1.17	11.42–16.18	<0.001		
			R		–17.8 ± 2.7	–8.2 ± 2.9	9.6 ± 0.99	7.58–11.62	<0.001		
		Rewarming to 36°C	L		–7.8 ± 3.0	–0.4 ± 3.2	7.4 ± 1.10	5.16–9.64	<0.001		
			R		–9.7 ± 2.5	–5.8 ± 2.8	3.9 ± 0.94	1.98–5.82	<0.001		
		Post-CPB	L		–4.7 ± 3.0	1.4 ± 2.8	6.1 ± 1.03	4.00–8.20	<0.001		
			R		–5.5 ± 2.6	–2.0 ± 3.1	3.5 ± 1.01	1.43–5.57	0.002		
		Skin closure	L		–3.5 ± 3.8	1.4 ± 3.2	4.9 ± 1.24	2.36–7.44	<0.001		
			R		–6.1 ± 2.9	–0.1 ± 3.3	6.0 ± 1.10	3.76–8.24	<0.001		
Sevoflurane-based anesthesia vs. propofol-based anesthesia	Schoen 2011									–	Test values directly compared* (AMT, Stroop Test, TMT, WL-N)
Norepinephrine during CPB vs. phenylephrine	Brassard 2014	Mean throughout CPB	–							–	–
		Diabetics		8 vs. 6	–8.0 ± 2.4	–8.0 ± 6.6	0 ± 2.50	–5.48–5.48	1.000		
		Nondiabetics		9 vs. 8	–4.0 ± 2.8	1.0 ± 4.3	5.0 ± 1.74	1.29–8.71	0.012		

Note:

- All values listed as percentage (%)
- Mohandas 2013: only means reported (no measure of variance); Vretzakis 2013: no control data; Kok 2014 and Schoen 2011: no intraoperative SctO₂ data
- *Lenkin 2013 data was reported as median (IQR)—mean and standard variation estimated
- *Difference between groups statistically significant (p < 0.05)

L, left; R, right; –, unclear/bifrontal/not reported; CI, confidence interval; CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; POCD, postoperative cognitive decline; ITT, intention-to-treat; SD, standard deviation; MMSE, mini-mental state examination; ASEM, antisaccadic eye movement test; AMT, abbreviated mental test; TMT, trail-making test; WL-N, word list recall test.

1. Cerebral oxygenation monitoring versus no monitoring (three RCTs).^{5,6,18} In two RCTs, the monitoring group was assigned a treatment intervention protocol to manage desaturations (below 75% of baseline). This protocol consisted of the use of interventions such as checking the patient's head position; adjusting ventilation to keep PaCO₂ above 40 mmHg; maintenance of mean arterial pressure (MAP) above 60 mmHg with administration of phenylephrine; adjustment of MAP to maintain cerebral perfusion pressure above 50 mmHg; increasing flow rate, if cardiac index was low; and administration of red blood cell transfusion, if hematocrit was low. The other RCT used NIRS monitoring as part of a blood transfusion protocol
2. Coronary artery bypass graft surgery with CPB versus without CPB (two RCTs)^{17,19}
3. Normothermic CPB versus hypothermic CPB (one RCT)¹⁶
4. Glyceryl trinitrate during pre-CPB and CPB versus placebo (one RCT)⁸
5. Midazolam as part of induction of anesthesia versus propofol (one RCT)²⁰
6. Sevoflurane anesthesia versus total intravenous anesthesia (one RCT)²¹
7. Sevoflurane-based anesthesia versus propofol-based anesthesia (one RCT)²²
8. Norepinephrine during CPB versus phenylephrine (one RCT).⁴

Among these, seven RCTs for seven interventions reported raw intraoperative SctO₂ and were included in the quantitative analysis. On visual inspection, five of these interventions (cerebral oxygenation monitoring driven management; normothermic CPB; glyceryl trinitrate during pre-CPB and CPB; midazolam in induction of anesthesia; and sevoflurane anesthesia) had a positive mean effect size of significance in the majority of measured time points with a maximum significant effect size of 15.0% ± 1.38% (*p* < 0.001) with glyceryl trinitrate post-CPB and a minimum significant effect size of 1.6% ± 0.14% (*p* < 0.001) with cerebral oxygenation monitoring.

On the other hand, one RCT¹⁷ appeared to show that surgery on pump has both positive and negative effects on SctO₂ compared to off pump depending on the time-point chosen for analysis during surgery. Additionally, the use of norepinephrine in CPB compared to phenylephrine for hemodynamic stabilization appeared to be beneficial for SctO₂ but only in nondiabetic patients, with no effect on diabetic patients.

Application of these study findings to clinical practice remains challenging. As there is only one study reporting raw intraoperative SctO₂ in the assessment of each of these interventions, detailed meta-analysis of the interventions is also not possible. Additionally, study sample sizes have generally been small exposing these studies to a high risk of type-I error and requiring validation in larger multicenter trials. Another challenge in interpretation of the literature has

been the measurement of the efficacy of such interventions on SctO₂, which has commonly been performed in a variety of ways. The majority of these studies were not designed based on raw changes in SctO₂ as their primary outcome and were therefore not powered to assess these changes. In particular, cerebral desaturation has been defined among our included studies separately as:

- A reduction of >15% from baseline
- Any negative change from baseline
- An area under the curve >10 minute%
- A reduction of >20% of the baseline or an absolute value below 50% for over a minute; a reduction of >30% of the baseline for over a minute
- A reduction of >20% of the baseline for over a minute, or
- An absolute value below 50%.

These definitions have been given with little direct clinical reasoning for their choice. Moreover, none of these values have been derived from appropriately controlled studies indicating a relationship of such desaturation with patient centered outcomes such as mortality or neuropsychological outcome. The authors, therefore, selected the most basic form of outcome (percentage saturation), to generalize our findings. However, given this limitation, and the clinical and methodological heterogeneity of these studies, it is difficult to compare the efficacy of each intervention directly.

This is the most up-to-date review of the literature regarding therapeutic interventions to optimize SctO₂. While the limitations imposed by the quality of research available may limit the scope of our findings, it clearly demonstrates the need for standardized definitions for cerebral oxygen desaturations both in the clinical and research settings. The authors believe that further research into these interventions and other potential interventions needs to be performed and that an evidence-based consensus needs to be reached about definitions for such desaturations, so that future studies may achieve a level of comparability.

POSTOPERATIVE CEREBRAL TISSUE OXYGEN SATURATION

While the impact of intraoperative cerebral oxygen desaturations has been studied, very little is understood about the etiology of POCD and the time course relationship between SctO₂ and POCD. In particular, SctO₂ monitoring is rarely continued postoperatively, despite the likely presence of ongoing physiological derangement. As a result, it is unclear whether desaturations intraoperatively persist during recovery in the ICU and while admitted to the surgical wards. The authors, therefore, sought to determine, from the reviewed RCTs, the trends for SctO₂ in the postoperative period of ICU and hospital admission, and whether postoperative cerebral oxygen desaturations are common and whether they have been associated with POCD.

Among the included RCTs, postoperative follow-up of SctO₂ was rare—only one RCT by Lenkin et al. measured and

reported postoperative SctO₂ up to 24 hours postoperatively.¹⁶ The results in this trial showed that for all measured time-points in this period, SctO₂ was significantly higher than baseline in both normothermic CPB and hypothermic CPB groups, with a p-value less than the α 0.05. While these results suggest that desaturation does not occur postoperatively, there are a number of confounding factors that may influence these results. In this study, patients in the normocapnic CPB and hypothermic CPB groups were admitted to the ICU for a median of 50 (IQR: 43–97) and 69 (IQR: 45–93) hours, respectively. As a result, the study authors believe that increased oxygen delivery is one of the key factors in these increased values. It remains unclear, how SctO₂ varies beyond this period when oxygen supplementation is weaned.

Furthermore, the extent to which variability in post-operative SctO₂ occurs as a consequence of the examined interventions in recovery is poorly understood. It is observed in the authors combined dataset that the final time-points measured in the perioperative period of each study commonly yielded results that showed desaturation of varying levels with the exception of the Lenkin study. This suggests that, more commonly, desaturation may in fact extend beyond the operating room, and that the application of therapeutic interventions may also be necessary in the ICU clinical setting. As a result, these findings indicate that, in trials of this nature, extended follow-up is warranted through at least the ICU admission to avoid later desaturations.

POSTOPERATIVE COGNITIVE DYSFUNCTION

The incidence of poor neurocognitive outcomes after cardiac surgery has been well documented in the literature. In particular, cerebral oxygen desaturation has been established as a predictor of POCD. In papers by Yao et al. and Slater et al., cerebral oxygen desaturations were independently associated with lower scores in the examined neurocognitive test battery.^{2,3} Therefore, establishment of clinical efficacy of therapeutic interventions seeking to prevent or treat intraoperative cerebral oxygen desaturations should involve assessment of POCD.

An important consideration in study designs assessing POCD is the choice of tests included as part of the neurocognitive test battery. Tests should cover a reasonable range of cognitive domains potentially affected by cardiac surgery. They should also be able to be performed both prior to surgery and after surgery within a reasonable amount of time, so that assessment is feasible and not inconvenient for both assessor and patient. It is important that the assessors are competent in the delivery of the tests, whether they are doctors, researchers, or trained in clinical neuropsychology; every effort should be made to avoid introducing operator bias or test-retest bias. The “Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery” provides a clear agreement about test principles and a series of tests that covers these considerations for the

purposes of both clinical assessment and research study designs.²³ The recommended test battery consists of:

- The Rey Auditory Verbal Learning Test—a test of short-term auditory verbal memory and rate of learning
- The Trail-Making Tests (A and B)—tests of visual attention and task switching
- The Grooved Pegboard Test—a test of manipulative dexterity.

Of the 11 RCTs in this review, four used neurocognitive test batteries in order to assess neuropsychological outcomes (Table 3). Two of these RCTs^{17,19} compared the incidence of POCD in bypass graft surgery with CPB to surgery without CPB, showing no significant difference between these two groups. However, their respective definitions of POCD and tests used varied significantly, resulting in one RCT having an equal incidence of 4% in the study groups, with the other having an incidence of 62 and 53% between groups. The other two RCTs^{5,22} did not define POCD as a patient outcome, but instead directly compared neurocognitive test scores, each showing a significant increase in test results between monitoring and no monitoring, and between sevoflurane-based anesthesia and propofol-based anesthesia.

Specific tests used in assessments performed in these RCTs included the mini-mental state examination, cogstate test battery, antisaccadic eye movement test, abbreviated mental test, trail-making tests, word list recall test, and the Stroop test.

Notably, each study appeared to test differing domains of cognitive function with an extremely wide variety of tests being used. Only one test used, the Trail-Making test was recommended by the aforementioned consensus statement suggesting a general disagreement between recommendations and actual research practice. This disconnect greatly limits the interpretation of the research findings as the inconsistency between tests used means that comparisons between studies are impossible, and renders any form of meaningful review of these outcomes somewhat ineffective. The authors therefore, recommend that researchers in this field use the original consensus statement in designing their studies or reach a new consensus upon which to base their research, so that interstudy consistency is maintained. This would improve the overall quality of the research and provide information that is more easily translatable into clinical practice.

STRENGTHS AND LIMITATIONS OF THE REVIEW

To the authors’ knowledge, this review is the first to meta-analyze and describe baseline SctO₂ in this patient cohort using data from RCTs. The authors search strategy was systematic and unlikely to introduce bias. It also provides the most up-to-date review of the literature on the use of NIRS in cardiac surgery patients. Their findings extend the understanding of baseline SctO₂ and trends during cardiac

surgery despite the significant clinical and methodological heterogeneity in the included studies.

However, this review has several limitations. The choice of including only outcome data presented as percentage saturation may have limited the inclusion of some studies with relevant findings. However, this was an unavoidable limitation given the wide range of definitions in each study for other outcome measures. The authors only considered RCTs for inclusion in this review, limiting their pool of studies and patients. However, the authors considered that RCTs would provide the most robust dataset for such assessment. Furthermore, English was a requirement of the search strategy and several studies were excluded on the basis of being published in a non-English language. However, neither of these strategies is likely to add bias to the review.²⁴

FUTURE DIRECTIONS

In this review, the authors identified 11 RCTs reporting relevant information, defining a pooled mean baseline SctO₂ of approximately 66%, and a wide reference range. Moreover, the authors found that a number of interventions appear to have a significant effect on raw intraoperative SctO₂, including SctO₂ monitoring-based management, normothermic CPB, glyceryl trinitrate during pre-CPB and CPB, midazolam in induction of anesthesia, and sevoflurane anesthesia. Finally, however, we also found that follow-up of postoperative SctO₂ and POCD was rare among these studies.

Given the wide range of baseline SctO₂ in cardiac surgery patients, future investigative studies must tackle several key gaps in knowledge. Firstly, large-scale studies in more uniform cardiac surgery populations are necessary to contextualize the results of individual patient. Despite the difficulty in validating NIRS readings to other measurements of cerebral oxygen supply and demand, the effect of patient characteristics and comorbid factors on baseline SctO₂ must be determined. This information will enable more personalized preoperative planning, given the increased patient risk associated with low-baseline SctO₂. Furthermore, future research measuring SctO₂ needs to adhere to measurement methods appropriate for the technology. These include measurement of both hemispheres in order to capture the varying physiology of each and baseline preoperative measurements taken before oxygen supplementation, which may increase SctO₂ artificially.

In assessing the efficacy of therapeutic interventions aiming to optimize SctO₂, a number of factors affect the applicability of study results. Cerebral tissue oxygen saturation should be measured prior to surgery, so that comparisons can be made with the baseline. Time-points of measurement during the perioperative period should be consistent across studies to allow for greater comparability between studies. Given the variable length of time of different cardiac surgical procedures, measurements at key time landmarks such as at induction of anesthesia, at the

commencement of CPB, at the cessation of CPB and at the end of the surgery are essential with other measurements taken 5 minutely in between these landmarks. Additionally, the wide range of definitions for desaturation creates challenges for the interpretation of studies—a consensus should be sought as to a particular score or measure of desaturation for consistency and this should be reported alongside the raw SctO₂ values for comparison before any further statistical model analysis. A strict definition as such would provide not only clearer interpretation of the research, but also clinical benefit for absolute reference values with which to diagnose intraoperative cerebral oxygen desaturation.

Additionally, the authors recommend that postoperative SctO₂ be measured more frequently to obtain a better understanding of the trends during mechanical ventilation and postextubation in the ICU or on the ward. This will give an indication as to the normal variability of SctO₂ in the recovery period as well as highlight the potential continuing effect of therapeutic interventions performed intraoperatively on long-term SctO₂ changes. If low SctO₂ values do indeed continue well beyond the initial postoperative period, this may also represent a target for therapeutic intervention in order to minimize preventable causes of POCD. The diagnosis of POCD continues to carry some difficulty with varying tests and definitions being used in tandem across both the clinical and research worlds. Despite the presence of clear recommendations and consensus between professionals, it is evident that, in order to improve the quality and validity of research, consistency is necessary in these areas. Therefore, researchers should consider these key principles when designing studies about SctO₂ in this patient cohort.

Many of the interventions assessed in these reviewed studies show promise for the future of cardiac surgical management. In particular, the intervention of standardized SctO₂ monitoring with a treatment intervention protocol as described by Murkin et al.⁶ The particular interventions employed by such protocol are simple, easily achievable, and designed in a systematic way. Each of the individual components, however, may provide further information for therapeutic targets, when used in isolation. Another component of this intervention protocol is the use of SctO₂ monitoring to activate blood transfusion.¹⁸ In order for these interventions to become part of standard practice, further larger cohort RCTs need to be performed to confirm the pilot study findings.

Additionally, targeting a higher PaCO₂ appears to be another potential therapeutic intervention in improving intraoperative SctO₂. Murkin et al. target PaCO₂ levels greater than 40 mmHg in their protocol, as carbon dioxide arterial tension is one of the major determinants of cerebral blood flow and changes in its partial pressure during and after CPB may affect cerebral blood flow.^{25,26} Increases to PaCO₂ have a vasodilatory effect on cerebrovascular tone and subsequently increases cerebral blood flow.²⁷ It is also known that PaCO₂ is significantly correlated with SctO₂. As all patients

requiring CPB are mechanically ventilated on admission to the ICU postsurgery, full control of PaCO₂ in both the intraoperative and postoperative periods should be possible in almost all patients and carries no additional cost.^{25,26} Hence, manipulation of PaCO₂ could be an easy and likely safe therapeutic intervention in cardiac surgery patients. In other areas, where patients have suboptimal cerebral blood flow, targeting a mild hypercapnia appears to be beneficial to both SctO₂ and cerebral protection. Across two trials by Eastwood et al.^{28,29} targeting mild hypercapnia in cardiac arrest patients were associated with an increase in SctO₂ as measured by NIRS as well as an attenuation in the release of neuron-specific enolase, a marker of cerebral injury. As it was shown to be feasible and safe in this patient cohort, further applications of therapeutic targeted mild hypercapnia appear warranted in areas such as cardiac surgery.

CONCLUSION

The authors aggregated data from RCTs measuring SctO₂ using NIRS in cardiac surgical patients and determined a pooled mean for normal preoperative SctO₂ values of approximately 66% with a reference range of 51–82%. Many of the therapeutic interventions assessed in these RCTs were shown to be beneficial in optimizing intraoperative SctO₂, although study validity may have been compromised by significant clinical heterogeneity and poor methodological quality. Unfortunately, the authors found that follow-up of postoperative SctO₂ was rare and that methods for the diagnosis of POCD were inconsistent. Nonetheless, there is increasing support for the use of NIRS in cardiac surgical patients in order to detect otherwise hidden cerebral oxygen desaturations. Further standardized research is indicated to relate intraoperative SctO₂ to normal preoperative values and to identify whether intra- and postoperative modulation of SctO₂ is associated with changes in POCD.

REFERENCES

- Anastasiadis K, Argiriadou H, Kosmidis MH, et al. Neurocognitive outcome after coronary artery bypass surgery using minimal versus conventional extracorporeal circulation: a randomised controlled pilot study. *Heart*. 2011;97(13):1082–8.
- Slater JP, Guarino T, Stack J, Vinod K, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thoracic Surg*. 2009;87(1):36–44.
- Yao F, Tseng C, Ho C, Levin S, et al. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2004;18(5):552–8.
- Brassard P, Pelletier C, Martin M, et al. Influence of Norepinephrine and Phenylephrine on Frontal Lobe Oxygenation During Cardiopulmonary Bypass in Patients with Diabetes. *J Cardiothorac Vasc Anesth*. 2014;28(2):608–17.
- Mohandas B, Jagadeesh A, Vikram S. Impact of monitoring cerebral oxygen saturation on the outcome of patients undergoing open heart surgery. *Ann Card Anaesth*. 2013;16(2):102–6.
- Murkin J, Adams S, Novick R, et al. Monitoring brain oxygen saturation during coronary bypass surgery: A randomized, prospective study. *Anesth Analg*. 2007;104(1):51–8.
- Severdijia EE, Gommer ED, Weerwind PW, Reulen JPH, Mess WH, Maessen JG. Assessment of dynamic cerebral autoregulation and cerebral carbon dioxide reactivity during normothermic cardiopulmonary bypass. *Med Biol Eng Comput*. 2015;53(3):195–203.
- Piquette D, Deschamps A, Bélisle S, Pellerin M, Levesque S, Tardif JC, et al. Effect of intravenous nitroglycerin on cerebral saturation in high-risk cardiac surgery. *Can J Anaesth*. 2007;54(9):718–27.
- Steppan J, Hogue CW Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol*. 2014;28(4):429–39.
- Dullenkopf A, Baulig W, Weiss M, et al. Cerebral near-infrared spectroscopy in adult patients after cardiac surgery is not useful for monitoring absolute values but may reflect trends in venous oxygenation under clinical conditions. *J Cardiothorac Vasc Anesth*. 2007;21(4):535–9.
- Schneider B, Abramo T, Albert G. An update on cerebral oxygenation monitoring, an innovative application in cardiac arrest and neurological emergencies. In: Vincent J, editor. *Annual Update in Intensive Care and Emergency Medicine* 2015. 1st ed. Switzerland: Springer International Publishing Switzerland; 2015. pp. 273–86.
- Bickler P, Feiner J, Rollins M. Factors affecting the performance of 5 cerebral oximeters during hypoxia in healthy volunteers. *Anesth Analg*. 2013;117(4):813–23.
- Scheeren T, Schober P, Schwarte L. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. *J Clin Monit Comput*. 2012;26(4):279–87.
- Nollert G, Möhnle P, Tassani-Prell P, et al. Determinants of cerebral oxygenation during cardiac surgery. *Circulation*. 1995;92(9 Suppl):II327–33.
- Heringlake M, Garbers C, Kabler J, et al. Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. *Anesthesiology*. 2011;114(1):58–69.
- Lenkin A, Zaharov V, Lenkin P, et al. Normothermic cardiopulmonary bypass increases cerebral tissue oxygenation during combined valve surgery: a single-centre, randomized trial. *Interact Cardiovasc Thorac Surg*. 2013;16(5):595–601.
- Negargar S, Mahmoudpour A, Taheri R, et al. The relationship between cerebral oxygen saturation changes and post operative neurologic complications in patients undergoing cardiac surgery. *Pak J Med Sci*. 2007;23(3):380–5.
- Vretzakis G, Georgopoulou S, Stamoulis K, et al. Monitoring of brain oxygen saturation (INVOS) in a protocol to direct blood transfusions during cardiac surgery: a prospective randomized clinical trial. *J Cardiothorac Surg*. 2013;8:145.
- Kok W, van Harten A, Koenen B, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass. *Anaesthesia*. 2014;69(6):613–22.
- Kim D, Kwak Y, Nam S, et al. Assessment of cerebral oxygen supply-demand balance by near-infrared spectroscopy during induction of anesthesia in patients undergoing coronary artery bypass graft surgery: comparison of midazolam with propofol. *Korean J Anesthesiol*. 2009;57(4):428–33.
- Guclu C, Unver S, Aydinli B, Kazanci D, et al. The Effect of Sevoflurane vs. TIVA on Cerebral Oxygen Saturation During Cardiopulmonary Bypass—Randomized Trial. *Adv Clin Exp Med*. 2014;23(6):919–24.
- Schoen J, Husemann L, Tiemeyer C, et al. Effect of intravenous nitroglycerin on cerebral saturation in high-risk cardiac surgery. *Can J Anaesth*. 2011;54(9):718–27.
- Murkin JM, Newman SP, Stump DA, et al. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Ann Thorac Surg*. 1995;59(5):1289–95.
- Morrison A, Polisena J, Husemann D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care*. 2012;28(2):138–44.
- Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Crit Care*. 2010;14(2):220.
- Yokoyama I, Inoue Y, Kinoshita T, et al. Heart and brain circulation and CO₂ in healthy men. *Acta Physiologica*. 2008;193(3):303–8.
- Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. *Anesthesiology*. 2015;122(1):196–205.
- Eastwood G, Schneider A, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation*. 2016;104:83–90.
- Eastwood G, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. *Resuscitation*. 2016;102:11–6.

Induced Hypothermia: Current Status—Benefits and Harms

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INTRODUCTION

Therapeutic hypothermia (TH) has been known to mankind since almost 3,000 years, from the time of Hippocrates, and has been used experimentally and clinically for the past 100 years. Evidence of its benefit in postcardiac arrest resuscitation was based on two randomized controlled trials (RCTs) published in the early 2000s.^{1,2} Following this, therapeutic hypothermia as a part of targeted temperature management (TTM) was included in most cardiac arrest resuscitation guidelines. A sequential trial analysis in 2011³ and subsequent RCT in 2013⁴ cast some doubts on the benefits of TTM. We will discuss the current status of TTM and its utilization in various clinical scenarios.

DEFINITIONS^{5,6}

Normal Body Temperature

In healthy individuals, in the age range of 18–40 years, the mean oral temperature of $36.8^{\circ}\text{C} \pm 0.4^{\circ}\text{C}$ ($98.2 \pm 0.7^{\circ}\text{F}$) is considered normal, with the lower limit in the morning and the upper limit in the evening. Rectal temperature is usually 0.5°C higher compared to oral temperature. Core body temperature can be measured at the following sites:

- Pulmonary artery
- Lower oesophagus
- Rectum
- Bladder
- Tympanic membrane.

Hypothermia

A core temperature of $<36^{\circ}\text{C}$ regardless of the cause is known as hypothermia. It may be:

- Mild: $33\text{--}36^{\circ}\text{C}$

- Moderate: $28\text{--}33^{\circ}\text{C}$
- Severe: $<28^{\circ}\text{C}$.

Induced Hypothermia

An intentional lowering of core body temperature to $<36^{\circ}\text{C}$ is known as induced hypothermia.

Therapeutic Hypothermia

Controlled induced hypothermia ($32\text{--}34^{\circ}\text{C}$) plus measures taken for controlling side effects like shivering is known as therapeutic hypothermia.

Targeted Temperature Management

Targeted temperature management has replaced the term therapeutic hypothermia and encompasses all the measures intended to keep temperature level below 37°C , including prevention of fever. Thus, the temperature spectrum of TTM ($32\text{--}36^{\circ}\text{C}$) includes TH ($32\text{--}34^{\circ}\text{C}$) and fever control (normothermia, approximate temperature 36°C).^{5,6}

TARGETED TEMPERATURE MANAGEMENT^{4,7}

Recent reports favor the use of the term TTM rather than therapeutic hypothermia to emphasize the importance of complete temperature profile. It comprises of three phases:

1. Phase of initiation or induction: It is the period required to intentionally achieve the lower temperature (target temperature) from the current body temperature. It should last not more than 1 hour and 30 minutes
2. Phase of maintenance: The target temperature at which the patient is kept for an extended period. It typically lasts 12–24 hours but may last several days

3. Phase of rewarming or reversion: It is the change of temperature from the maintenance phase to near normal temperature by gradually increasing the temperature at a specific rate or allowing the body to achieve intrinsic physiologic body temperature. Rewarming should not be at a rate $>0.1-0.25^{\circ}\text{C/h}$.

Side Effects During Phases of Targeted Temperature Management⁵⁻⁸

- Phase of initiation or induction: Shivering
- Phase of maintenance: Bradycardia, insulin resistance causing hyperglycemia, polyuria, hypokalemia, infections, coagulopathy (due to abnormal function and decrease in the number of platelets)
- Phase of rewarming or reversion: Shivering, hypoglycemia, and hypotension.

Treatment of Side Effects of Targeted Temperature Management⁹

- Shivering: Acetaminophen, skin counter warming, buspirone, magnesium, meperidine, dexmedetomidine, fentanyl, propofol, midazolam, neuromuscular junction blockers
- Bradycardia: No treatment needed
- Insulin resistance causing hyperglycemia: Insulin as infusion to maintain plasma glucose between 140 mg/dL to 180 mg/dL
- Polyuria: Fluid replacement
- Hypokalemia: Replace potassium as needed
- Infections: Screening to detect infections and antibiotics as needed
- Coagulopathy: Transfusions if significant bleeding occurs
- Hypoglycemia: Dextrose infusions as needed
- Hypotension: Fluid replacement and vasopressors.

Methods of Cooling¹⁰

These are divided into methods used for surface or core cooling:

- A. Surface cooling
 - Fans
 - Ice packs
 - Refrigerated surface or cooling pads
 - Cooling blankets: circulating either air or water
 - Immersion of patient in cold water.
- B. Core cooling
 - Infusion of cold saline (cooled to 4°C) and infused at a rate of 30 mL/kg/h, up to a total of 1.5–3 L
 - Intravascular ice saline-filled balloon catheter
 - Heart-lung bypass machine
 - Peritoneal lavage machine.

EVIDENCE FOR THE USE OF TARGETED TEMPERATURE MANAGEMENT IN VARIOUS CLINICAL SETTINGS

Cardiac Arrest

Out-of-hospital Cardiac Arrest^{1,2,5,7,8-12}

The two most influential studies published in 2002 provide the most compelling evidence about the benefit of therapeutic hypothermia in out-of-hospital cardiac arrest (OHCA). Following these articles, interest and research in therapeutic hypothermia and TTM increased exponentially.

Bernard et al., 2002:

- Single center trial
- Conducted in Australia
- Patients enrollment: 77 adult patients with OHCA with shockable rhythm, i.e., ventricular fibrillation (VF) who had postcardiac arrest syndrome (PCAS), i.e., were comatose having no meaningful response to verbal commands
- Patient groups: Patients were assigned to receive either normothermia or therapeutic hypothermia [target temperature 33°C , initiated in ambulance after return of spontaneous circulation (ROSC), for duration of 12 hours after hospitalization]
- Outcomes were assessed at hospital discharge
- Results: More patients in the therapeutic hypothermia group had favorable neurological outcomes at hospital discharge than the patients in the normothermia group [49% compared to 26%; $p = 0.046$; (OR 5.25; 95% CI 1.47–18.76; $p = 0.011$)]. However, mortality in both the groups was not different
- Criticism of the trial: There was inadequate process of randomization as patients were randomized to therapeutic hypothermia group on odd days and to normothermia group on even days. Also, if any patient in the normothermia group was found to have temperature below 37.4°C , they were warmed to raise their temperature.

The Hypothermia after Cardiac Arrest (HACA) trial, 2002:

- Multicentric trial
- Conducted in Europe
- Patients enrollment: 275 adult, comatose patients surviving a witnessed OHCA presumed to be of cardiac origin with shockable initial rhythm, either VF or ventricular tachycardia (VT)
- Patient groups: Patients were randomly assigned to two groups, one received standard treatment with normothermia and the other group got therapeutic hypothermia (at a target temperature of $32-34^{\circ}\text{C}$, initiated at hospital after ROSC, for duration of 24 h).
- Outcomes were assessed at 6 months (neurological outcomes and mortality)

- Results: At 6 months, therapeutic hypothermia group had both better neurological outcomes (Glasgow-Pittsburgh cerebral performance category of 1 or 2) compared to the standard treatment group [55% compared to 39%; $p = 0.09$ —respiratory rate (RR) 1.4; 95% confidence interval (CI) 1.08–1.81]. Also, there was lower mortality at 6 months in the therapeutic hypothermia group [41% compared to 55%; (RR 0.74; 95% CI 0.58–0.95)]
- Criticisms of the trial: Recruitment for the trial was very slow. Only 8% of the screened patients were recruited in the actual study, leading to eventual termination of the trial. Predefined power calculation was lacking. Temperature control in normothermia group was not strict with average temperature almost 38°C as many patients had fever which was not adequately controlled. Also, preintervention Glasgow Coma Scale (GCS) was not recorded and there was nonstandardized withdrawal of support which may have lead to potential bias in the measured primary outcomes.

*International Liaison Committee
on Resuscitation Statement, 2010:*

- Patients with OHCA who had initial cardiac rhythm in the form of VF or VT should undergo TTM after ROSC and if having post-cardiac arrest syndrome (PCAS)
- Patients with OHCA who had initial cardiac rhythm in the form of asystole or pulseless electrical activity (PEA) and patients with inhospital cardiac arrest (IHCA) may undergo TTM after ROSC and if having PCAS
- Target temperature for TTM should be 32–34°C
- The duration of therapeutic hypothermia should be 12–24 hours. After these recommendations, TTM was accepted as the standard of care in PCAS by various professional societies.

Neilsen et al., 2011:

The evidence generated by therapeutic hypothermia, RCTs was reviewed using meta-analysis and trial sequential analysis found the evidence in support of therapeutic hypothermia was of low quality.

Arrich et al., Cochrane Review, 2012:

- They reviewed evidence presented in five RCTs and concluded that amongst the 481 patients included in these trials, in patients with cardiac arrest who had ROSC, mild therapeutic hypothermia improved survival led to better neurological outcomes.
- Criticism of the Cochrane review, 2012 on therapeutic hypothermia: Two RCTs had baseline differences in their two groups of patients, whereas in two other trials, investigators were not adequately blinded to the interventions leading to potential bias.

Neilsen et al., 2013:

- Large multicentric trial

- Conducted in Europe and Australia
- Presented conflicting evidence as compared to previous trials
- Patient enrollment: 939 patients of OHCA with presenting rhythm of either VF or VT, PEA or asystole who had ROSC and PCAS
- Patient groups: patients were randomly assigned to receive TTM at either 33°C or 36°C for duration of 28 hours followed by fever prevention for next 48 hours (i.e., 72 h of the cardiac arrest). Patients in the 33°C group had a target temperature of 33°C, with therapeutic hypothermia initiated at hospitalization after ROSC, for duration of 28 hours. Patients in the 36°C group received normothermia and strict fever control. After 72 hours a neurologist, blinded to the intervention received, would order continuity of care or withdrawal of treatment based on prognostic predictors of poor outcome [myoclonus, non-N20 response on somatosensory evoked potential (SSEP), no motor or pupillary response]
- Results: There was no difference in the neurological outcomes and mortality in the two groups. About 50% of patients in the 33°C group compared to 52% in the 36°C survived (hazard ratio 1.06; 95% CI 0.89–1.28; $p = 0.51$). At 6 months follow-up, 54% patients in the 33°C group had not survived or had poor neurological outcome compared to 52% patients in the 36°C group (RR 1.02; 95% CI 0.88–1.16; $p = 0.78$). In the subgroup of patients with VF or VT (80% of enrolled patients) as well, there was no difference in the two groups regarding benefit of TTM
- Criticisms of the trial: The difference of temperature in the two groups was not large enough compared to the trials showing benefit (3°C compared to 4–4.5°C). Patients with unshockable rhythm were included.

Kim et al., 2014:

They studied prehospital application of therapeutic hypothermia after ROSC in patients with OHCA with presenting rhythm VF or non-VF. Compared to therapeutic hypothermia applied at hospital, there was no benefit in neurological outcomes or mortality.

Debaty et al., 2014:

They studied use of intracardiac arrest therapeutic hypothermia in patients with OHCA with any presenting rhythm. Patients were randomized to undergo therapeutic hypothermia at site of cardiac arrest or after reaching hospital. There was no difference in the groups with regards to neurological outcomes or mortality at 1 month after cardiac arrest.

Zhang et al., 2015:

- They undertook a systemic review and meta-analysis of six RCTs including 1,417 patients, almost half of whom were treated with TTM

- They studied the effect of mild-induced hypothermia (MIH) (target temperature $\leq 34^{\circ}\text{C}$), in patients with cardiac arrest (OHCA or IHCA)
- Results: No significant reduction in mortality due to MIH at discharge from hospital or at 6 months was found. However, there was reduction in mortality of cardiac arrest patients with shockable rhythm at discharge from hospital or at 6 months. Neurological outcomes were improved in patients with shockable rhythm at hospital discharge but not after 6 months. There was a higher incidence of complications in the MIH group. Trial sequential analysis could not confirm or reject the effect of the intervention.

Inhospital Cardiac Arrest¹³

Mikkelsen et al., 2013:

- A cohort study conducted in the United States
- Studied the use of therapeutic hypothermia in IHCA in a large number of hospitals
- Results: Therapeutic hypothermia was used in a very small number of patients (2%) and in half of these patients, it was used improperly (target temperature over or under achieved).

Traumatic Brain Injuries^{5,8,9,14-16}

Clifton et al., 1993:

- A phase II trial
- It showed improvement in therapeutic hypothermia therapeutic hypothermia group.

Marron et al., 1997:

- Randomized controlled trials
- Patients enrolled: A total of 84 patients with severe traumatic brain injuries (TBI)
- Patient groups: Standard care group or mild hypothermia group (target temperature 33°C for duration of 24 h)
- Results: In patients with GCS of 5–7 at hospitalization, there was significant neurologic improvement at 3 and 6 months in the mild hypothermia group.

Clifton et al., 2001:

- Also known as the North American Brain Injury Study: Hypothermia (NABIS:H) trial
- Large, multicentric RCT
- Patients enrolled: A total of 392 patients of all types of severe acute brain injury, in the age range 16–65 years
- Patient groups: Normothermia (37°C) or surface cooling induced therapeutic hypothermia [therapeutic hypothermia started within 2–5 h of brain injury (early hypothermia), target temperature 33°C , for duration of 48 h]

- Results: No significant difference in neurological outcomes (57% in both the groups) and mortality (28% therapeutic hypothermia group and 27% normothermia group) in both the groups. Thus, therapeutic hypothermia was inefficacious in TBI. On subanalysis, it was found that patients who were hypothermic on hospital admission had improved outcomes, though the evidence was weak.

Jiang et al., 2006:

- Randomized controlled trials
- Patients enrolled: A total of 215 patients with severe TBI
- Patient groups: Patients randomized to receive therapeutic hypothermia at target temperature $33\text{--}35^{\circ}\text{C}$ with cooling blankets for 48 hours (conventional therapeutic hypothermia) or >48 hours to 5 days (prolonged therapeutic hypothermia)
- Results: Patients in prolonged therapeutic hypothermia group had better neurological outcomes.

Kramer et al., 2009, Cochrane review:

- It included 23 trials for a total of 1,614 patients who received early therapeutic hypothermia at target temperature 35°C for 12 hours
- Patients treated with therapeutic hypothermia had better neurological outcomes and lower mortality
- However, the studies showing statistical significance had methodology of poor quality.

Clifton et al., 2011:

- It is also known as the NABIS:H II trial
- Randomized controlled trials
- Patients enrolled: A total of 97 patients of all types of severe TBI in the age range 16–45 years, presenting within 2.5 hours of the injury
- Patient groups: Normothermia (37°C) or therapeutic hypothermia [therapeutic hypothermia started within 2–5 hours of brain injury (early hypothermia), target temperature 33°C , for duration of 48 h]
- Results: There was nonsignificant improvement in neurological outcomes (60% compared to 57%) as well as mortality (23% compared to 18%) in the therapeutic hypothermia group compared to normothermia group. In a subgroup of patients with hematoma which was surgically evacuated, there was significant improvement with early induced hypothermia

Maekawa et al., 2015:

- It is also known as the brain-hypothermia (B-HYPO) trial
- Multicentric RCT
- Patients enrolled: A total of 148 patients with TBI in the age range 15–70 years
- Patient groups: Fever control group ($35.5\text{--}37^{\circ}\text{C}$) or mild prolonged therapeutic hypothermia (target temperature $32\text{--}34^{\circ}\text{C}$, for duration of 72 hours followed by rewarming at the rate of $<1^{\circ}\text{C}/\text{day}$)

- Results: There was no significant improvement in neurological outcomes (RR 1.24; 95% CI 0.62–2.48; $p = 0.597$) or mortality (RR 1.82; 95% CI 0.82–4.03; $p = 0.180$) in the therapeutic hypothermia group compared to fever control group.

Suehiro et al., 2015:

In a secondary analysis of the B-HYPO trial results, TBI patients with hematoma who were young (age <50 years) and who had the hematoma surgically evacuated, had significant improvement with mild prolonged hypothermia.

Refractory Intracranial Hypertension and Brain Edema^{15,16}

Sadaka et al., 2012:

A systematic review of 13 RCTs and 5 observational studies of patients with TBI with intracranial hypertension and who underwent treatment with therapeutic hypothermia. There was significant reduction in intracranial pressure.

EUROTHERM3235:

- Ongoing RCT
- 1,800 patients with primary closed TBI with elevated intracranial pressure >20 mmHg
- Patient groups: Patients were randomized to two groups. One group received standard treatment and the other group underwent therapeutic hypothermia at 32–35°C for period of 48 hours and further as necessary to maintain intracranial pressure (ICP) <20 mmHg
- Preliminary results: There was better outcome in the TTM group for controlling refractory intracranial hypertension.

Stroke^{5,9,14-16}

Ischemic Stroke

Animal experimental studies: Therapeutic hypothermia is beneficial in animal models with therapeutic hypothermia. It was found to reduce both infarct size and neurological outcomes with earlier initiation of therapeutic hypothermia leading to reduced infarct size.

Schwab et al., 1998:

- Case series
- Patients enrolled: Patients of stroke with middle cerebral artery occlusion leading to hemispheric infarction and out of window period for thrombolysis
- A total of 25 patient received TTM (target temperature 33°C for duration of 48–72 h with slow rewarming). Targeted temperature management was delivered by surface cooling
- Result: There was significant reduction in mortality in TTM group as compared to natural history data.

Guluma et al., 2006:

They demonstrated that TTM was feasible and safe in awake, spontaneously breathing stroke patients using an endovascular device.

Els et al., 2006:

- Randomized controlled trials
- Patients enrolled: A total of 25 patients with hemispheric ischemic stroke were enrolled
- Patient groups: Randomized to hemicraniectomy alone or hemicraniectomy with therapeutic hypothermia
- Results: There was statistically nonsignificant additional benefit of therapeutic hypothermia in patients undergoing hemicraniectomy who had malignant ischemic stroke.

Hemmen et al., 2010:

- It is also known as intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS) trial
- Randomized controlled trials
- Result: The trial demonstrated safety and feasibility of these therapies together, but here was no benefit of adding therapeutic hypothermia to thrombolysis in acute ischemic stroke
- Criticisms of the trial: The trial was underpowered to demonstrate benefit of therapeutic hypothermia.

Hemorrhagic Stroke

Animal experimental studies: No benefit was demonstrated of therapeutic hypothermia for improving neurological outcomes in patients with intracranial hemorrhage.

Den Hertog et al., Cochrane Review, 2009:

- It included six RCTs and two other trials
- Therapeutic hypothermia has no significant beneficial effect in the treatment of ischemic or hemorrhagic stroke.

Kollmar et al., 2010:

- A case series
- It studied the effect of therapeutic hypothermia (35°C for 10 days) in 12 patients with spontaneous intracranial hematoma
- Result: There was significant benefit in the reduction of perilesional edema.

Acute Liver Failure and Hepatic Encephalopathy^{5,8,14}

Jalan et al., 1999, 2003, 2004: In a total of 36 patients over 3 case series, demonstrated benefit of TTM to lower ICP and act as bridge to liver transplantation.

Sepsis^{8,14}

Animal experimental studies: Beneficial effect was demonstrated of therapeutic hypothermia in animal models of sepsis reducing bacterial dissemination and acute lung injury and increasing period of survival.

Schortgen et al., 2012:

- Multicentric RCT
- Patients enrolled: A total of 200 patients with septic shock having fever, on mechanical ventilation and requiring vasopressors and sedation
- Patients groups: Patients randomized to receive standard therapy or TTM (external cooling to target temperature 36.5–37°C for duration of 48 h)
- Results: There was significant reduction in surface body temperature, vasopressor dose at 12 hours and 14 days mortality in patients in the TTM group.

Meningitis⁵

Mourvillier et al., 2013:

- Multicentric RCT
- Patients enrolled: A total of 98 patients with bacterial meningitis and coma were recruited
- Patients groups: Patients randomized to receive standard therapy or TTM (with intravenous bolus infusion of cold saline at 4°C, target temperature 32–34°C for duration of 48 h, and passive rewarming)
- Results: There was increased mortality in the TTM group (51% compared to 31%, $p = 0.04$) and the trial was prematurely terminated.

Spinal Cord Injury^{5,17}

Animal experimental studies: Therapeutic hypothermia (both locally applied and systemic) has beneficial effect in spinal cord injury (SCI) offering neuroprotection.

Romodanov et al.

In the spinal cord hypothermia study, 113 patients received applied hypothermia during spinal cord neurosurgery and found it to have beneficial intraoperative and postoperative effects.

Hayes et al., 1993:

Applied mild therapeutic hypothermia in patients with compressive and conductive SCI and found improvement in cortical evoked potential.

Levi et al., 2009:

The demonstrated that therapeutic hypothermia through an endovascular catheter was safe and feasible in patients with acute cervical SCI.

Madhavan et al., 2012:

They demonstrated improvement in injury scores with mild therapeutic hypothermia (target temperature 33°C for 24 h and slow rewarming in 5 patients with iatrogenic SCI.

Dididze et al., 2013:

In a case-control study of 35 acute cervical SCI patients applied mild therapeutic hypothermia (using intravascular catheter, target temperature 33°C for 48 hours, rewarming at 0.1°C/h) and found it to have beneficial effect leading to improvement.

Myocardial Infarction^{5,8,14,18}

Animal experimental studies: Conducted before reperfusion therapy era showed reduction in infarct size with therapeutic hypothermia.

Early clinical studies by Dixon et al., 2002 and Lye et al., 2005 were for providing proof of concept, assessment of feasibility and safety.

Gotberg et al., 2010:

- It was known as the rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction (Rapid MI-CE) trial.
- A pilot study
- A total of 18 patients with MI underwent therapeutic hypothermia (target temperature 33°C, duration 3 h, rewarming 3 h) prior to reperfusion
- Results: Application of therapeutic hypothermia did not delay reperfusion. Adequate therapeutic hypothermia was achieved in all patients. There was reduction in infarct size and no heart failure in therapeutic hypothermia group.

Grines et al., 2012:

- It was known as intravascular cooling adjunctive to percutaneous coronary intervention (PCI; part I) intravascular cooling adjunctive to primary coronary intervention (ICE-IT-I) trial
- Randomized controlled trials
- Patients enrolled: Total of 228 patients with MI
- Patient groups: Patients were randomized to two groups. One group received standard reperfusion therapy and the other received TTM (using cold saline and endovascular cooling) and reperfusion therapy
- Results: There was no evidence of benefit of TTM except slight reduction in infarct size in anterior wall infarcts.

Erlinge et al., 2013:

- Pooled analysis of the Rapid MI-CE and another unpublished trial
- Results: Patients with inferior and anterior infarct reaching target temperature at the time of reperfusion had reduction in infarct size.

Erlinge et al., 2014:

- It was known as efficacy of endovascular catheter cooling combined with cold saline for the treatment of acute myocardial infarction (CHILL-MI) trial
- Multicentric RCT
- Patients were randomized to receive therapeutic hypothermia (using endovascular device, target temperature 33°C for duration of 1 h) started prior to reperfusion or only reperfusion
- Results: A quarter of the patients failed to reach temperature <35°C prior to reperfusion. There was increased delay in starting reperfusion therapy and failure to reduce infarct size in the therapeutic hypothermia group. But the size of anterior wall infarctions and heart failure at 45 days was reduced.

Erlinge et al., 2015:

Pool analysis of Rapid MI-CE and CHILL-MI trials. Therapeutic hypothermia was found to be more effective when large area of at-risk myocardium is present, more effective in anterior wall MI and reduced heart failure.

Nichol et al., 2015:

- The evaluation of ultrafast hypothermia before reperfusion in ST segment elevation myocardial infarction patients (VELOCITY) trial used a peritoneal lavage device for TH
- Results: With the device, there was rapid and adequate cooling but there was delay in initiation of reperfusion, failure to reduce infarct size, increase in stent thrombosis, and other major adverse events.

Trauma⁵

There are no RCTs which support therapeutic hypothermia in trauma patients.

Acute Respiratory Distress Syndrome^{8,14}

Villar et al., 1993: Randomized controlled trial, 19 patients with septic acute respiratory distress syndrome (ARDS) who are mechanically ventilated and randomized to receive conventional treatment or TTM (32–35°C) with conventional treatment. There was reduction of mortality in the TTM group (67% compared to 100%).

Dillon et al. in 2015 published a case report of use of TTM in lung contusion related ARDS.

Hypoxic Ischemic Encephalopathy^{5,8,14}

Shankaran et al., 2005:

- Randomized controlled trial of infants who suffered moderate to severe hypoxic ischemic encephalopathy (HIE)
- Patient groups: Infants were randomized to therapeutic

hypothermia (target temperature 33.5°C, duration 72 h), and usual care

- Results: Targeted temperature management reduced disability at 2 years and mortality significantly.

Gluckman et al., 2005:

- Randomized controlled trial of neonates who suffered moderate to severe HIE
- Patient groups: Neonates randomized to usual care or TTM group (selective head cooling, target temperature 34–35°C, duration 72 h)
- Results: No significant difference in the disability at 2 years or mortality amongst the two groups, except in patients with moderately abnormal electroencephalogram, in whom there was benefit with TTM.

Azzopardi et al., 2009:

- Randomized controlled trial, which enrolled 325 infants with HIE
- Patient groups: Infants were randomized to usual care or TTM
- Results: There was no difference in the two groups with regard to death or disability.

Jacobs et al., 2013, Cochrane Review:

Eleven RCTs with 1,505 infants who had suffered HIE. It stated that TTM was beneficial in term infants with HIE.

CURRENT STATUS OF TARGETED TEMPERATURE MANAGEMENT/ THERAPEUTIC HYPOTHERMIA IN VARIOUS CLINICAL SCENARIOS⁷

Out-hospital Cardiac Arrest

Target temperature management is recommended in the treatment of OHCA especially when the initial rhythm is VT or VF. Target temperature management is the standard of care in patients with OHCA. These patients should undergo TH at hospitalization (target temperature 33°C) within 4 hours of cardiac arrest for duration of 24–48 hours. After therapeutic hypothermia, fever control should be instituted for at least 72 hours after the cardiac arrest.

In patients with OHCA when initial rhythm is asystole or PEA, TTM may be used but evidence for its use is not robust. Also, there is no recommendation for its use in IHCA.

Traumatic Brain Injuries

Efficacy of TTM in the management of TBI has not been demonstrated in large RCTs. However, reduction in secondary brain injury may be reduced by early, preoperative TH (animal experimental research and subanalysis of RCT). Hence, TTM may be considered in patients with TBI and raised ICP, in addition to other therapies. There should be

early initiation (<2.5 h), prolonged duration (>48 h), and very slow rewarming (<1°C/day).

Refractory Intracranial Hypertension and Brain Edema

Target temperature management is an effective, safe, and promising treatment strategy for controlling ICP in refractory intracranial hypertension and TBI.

Stroke

Sufficient evidence is not present to advocate the use of TTM in patients with stroke (ischemic or hemorrhagic).

Acute Liver Failure and Hepatic Encephalopathy

There is no large body of evidence to support the use of TH in patients with acute liver failure and hepatic encephalopathy. Randomized controlled trials in these patients will answer whether TTM is of use in the management of above patients.

Sepsis

Target temperature management is not recommended in the treatment of sepsis.

Meningitis

Target temperature management is not recommended for the treatment of patients with bacterial meningitis and in fact TTM has been found to be harmful in patients with bacterial meningitis.

Spinal Cord Injury

In SCI patients, benefit of TH has been demonstrated in limited number of patients. Large, well designed RCTs in these patients are needed. At present, there is lack of sufficient evidence to recommend TTM for the treatment of SCI.

Myocardial Infarction

Target temperature management is not recommended in the treatment of MI. Well-conducted and adequately powered RCTs are required.

Trauma

Target temperature management is not recommended in the treatment of trauma.

Acute Respiratory Distress Syndrome

Target temperature management is not recommended in the treatment of ARDS. Randomized controlled trials are

required to assess the potential of TTM as a treatment strategy in ARDS.

Hypoxic Ischemic Encephalopathy

Target temperature management is recommended in the treatment of neonatal HIE and is the standard of care.⁷

CONCLUSION

The role of TTM is evolving. Target temperature management is recommended in OHCA, refractory raised ICP and neonatal HIE. Target temperature management is to be used judiciously and only in the clinical scenarios in which it is recommended. Its use in other clinical setting should be restricted to clinical trial.

REFERENCES

- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-63.
- Holzer M, Cerchiari E, Martens P, et al. (Hypothermia after Cardiac Arrest Study Group). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-56.
- Nielsen N, Friberg H, Gluud C, et al. Hypothermia after cardiac arrest should be further evaluated – a systematic review of randomised trials with meta-analysis and trial sequential analysis. *Int J Cardiol*. 2011;151(3):333-41.
- Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013;369(23):2197-206.
- Saigal S, Sharma JP, Dhurwe R, et al. Targeted temperature management: Current evidence and practices in critical care. *Indian J Crit Care Med*. 2015;19(9):537-46.
- Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101-20.
- Nunnally ME, Jaeschke R, Bellington GJ, et al. Targeted temperature management in critical care: A report and recommendations from five professional societies. *Crit Care Med*. 2011;39(5):1113-25.
- Perman SM, Goyal M, Neumar RW, et al. Clinical Applications of Targeted Temperature Management. *Chest*. 2014;145(2):386-93.
- Kuroda Y. Neurocritical care update. *Journal of Intensive Care*. 2016;4:36.
- Vaity C, Al-Subaie N, Cecconi M. Cooling techniques for targeted temperature management post-cardiac arrest. *Critical Care*. 2015;19:103.
- Fukuda T. Targeted temperature management for adult out-of-hospital cardiac arrest: current concepts and clinical applications. *Journal of Intensive Care*. 2016;4:30.
- Zhang XW, Xie JF, Chen JX, et al. The effect of mild induced hypothermia on outcomes of patients after cardiac arrest: a systematic review and meta-analysis of randomised controlled trials. *Critical Care*. 2015;19:417.
- Mikkelsen ME, Christie JD, Abella BS, et al. Use of therapeutic hypothermia after in-hospital cardiac arrest. *Crit Care Med*. 2013;41(6):1385-95.
- Corry JJ. Use of hypothermia in the intensive care unit. *World J Crit Care Med*. 2012;1(4):106-22.
- Yokobori S, Yokota H. Targeted temperature management in traumatic brain injury. *Journal of Intensive Care*. 2016;4:28.
- Andresen M, Gazmuri JT, Marin A, et al. Therapeutic hypothermia for acute brain injuries. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*. 2015;23:42.
- Wang J, Pearse DD. Therapeutic hypothermia in spinal cord injury: The status of its use and open questions. *Int J Mol Sci*. 2015;16(8):16848-79.
- Kang IS, Fumiaki I, Pyun WB. Therapeutic hypothermia for cardioprotection in acute myocardial infarction. *Yonsei Med J*. 2016;57(2):291-7.

Management of the Brain-dead Organ Donor

Mohan A Mathew

INTRODUCTION

The definition of death of an organism has been diversified among various cultures, as per Indian mythology "Death is separation of soul (Atman) from body, where it goes through the cycle of birth-death-rebirth and ultimately merges with the universe (Brahman)". In Biblical terms, "God created man (Adam) out of the dust of the earth and inspired the breath of life into his nostrils and a man became a living soul then the dust will return to the earth as it was, and the spirit will return to God who gave it" (Ecclesiastes 12:7). Whereas the concept of brain death has been developed with the development of organ transplantation. By definition, brain death is a total irreversible cessation of functioning of the brain. The American Association of Neurology has defined brain death with three cardinal signs, cessation of the functions of the brain including the brainstem, coma, or unresponsiveness and apnea.¹

CLINICAL DIAGNOSIS OF BRAIN DEATH

It can be described under following headings:

- Establishing the cause of disease
- Excluding certain potentially reversible syndromes that may produce signs similar to brain death
- Demonstrating clinical signs of brain death: coma, brainstem areflexia, and apnea.

Establishing the Cause of Disease

Brain death can occur when the blood and/or oxygen supply to the brain is stopped. This can be caused by:

- Cardiac arrest
- Stroke
- Severe head injury
- Intracranial hemorrhage
- Infections (e.g., encephalitis)
- Brain tumor.

Confounding Factors

There are multiple confounding factors those need to be excluded before diagnosing brain death (Table 1).

Demonstrating Clinical Signs of Brain Death

Coma

The patient should be in coma and scored as 3 on the Glasgow Coma Scale. Motor responses of the limbs or facial muscles to painful supraorbital pressure should be absent. Motor responses (i.e., the Lazarus sign) may occur spontaneously during apnea testing and are considered to have a spinal origin. This sign is often observed during hypoxic or hypotensive episodes.

Brainstem Areflexia

The following reflexes should be demonstrated:

- Pupils nonreactive to bright light
- Cornea reflex absent
- Oculocephalic reflex absent (tested only if C-spine integrity ensured)

TABLE 1 Prerequisites before diagnosing brain death

Central nervous system (CNS)	• Absence of CNS depressant drugs (if required toxicology screening should be done)
Respiratory system	• Absence of spontaneous breaths • Absence of residual paralytics (nerve stimulator to be used in case of suspicion)
Cardiovascular system	• Absence of significant hypotension
Endocrine system	• Absence of severe endocrine disorders
Metabolic factors	• Absence of severe electrolyte disturbances • Absence of hypothermia (temperature <36°C) • Absence of severe acid-base disorders

- Oculovestibular reflex absent
- No facial movement to noxious stimuli at supraorbital nerve or temporomandibular joint
- Gag reflex absent
- Cough reflex absent to tracheal suctioning
- Absence of motor response to noxious stimuli in all four limbs
- Spinally mediated reflexes are permissible.

Apnea Test

Patient should be hemodynamically stable before doing apnea test. Ventilator settings are adjusted to provide normocarbica [partial arterial pressure of carbon dioxide (PaCO_2) 34–45 mmHg]. Patient preoxygenated with 100% fraction of inspired oxygen concentration (FiO_2) and positive end-expiratory pressure (PEEP) of 5 cmH_2O for more than 10 minutes to increase partial arterial pressure of oxygen (PaO_2) more than 200 mmHg. Provide oxygen via a suction catheter to the level of the carina at 6 L/min then disconnect ventilator watch for absence of spontaneous respirations, arterial blood gas drawn at 8–10 minutes, patient reconnected to ventilator and apnea is considered to be positive if PCO_2 more than 60 mmHg or 20 mmHg rise from normal baseline value.

Role of Auxiliary Tests

Only to be performed if clinical examination cannot be fully performed because of patient factors or if apnea testing inconclusive or aborted. The following tests are usually considered:

- Cerebral angiogram
- Single-photon emission computed tomography
- Electroencephalogram
- Transcranial Doppler.

NEED FOR BRAIN-DEAD DONOR MANAGEMENT

The most common obstacle in conducting organ transplant is the availability of donor organ, leading to an exponential increase in the waiting list of potential transplant recipients.² Organ donation statistics in India are not exciting, lack of public awareness, cultural and social issues are some of the issues associated with it. In India, the deceased donor organ donation rate is only 0.5 per million, while in USA at 25.6 per million and 18.3 per million in the United Kingdom.^{3–5} The provisional state-wide organ donation statistics for the year 2015 is given in table 2.

PATHOPHYSIOLOGY OF BRAIN DEATH^{6,7}

Cardiovascular System

Hemodynamic consequences associated with brain death are related to processes occurring during ischemic insult to brainstem [most often due to raised intracranial pressure (ICP) leading to cerebral herniation through the tentorium], these responses are as a result of complex interplay among neurohumoral, hormonal, and proinflammatory mechanisms. Clinically observed hemodynamic changes can be of two distinct phases, i.e., progressive ischemic phase and brainstem death completion phase.

TABLE 2 Deceased organ donation statistics—2015

State	No. of donors	*ODR (pmp)	Kidney	Liver	Heart	Lung	Pancrease	Intestine	Hand	Larynx	Total organs
Tamil Nadu	155	2.1	290	149	51	28	0	1	0	0	519
Kerala	76	2.3	132	61	14	2	1	1	4	1	216
Maharashtra	60	0.5	106	51	5	0	0	0	0	0	222
Telangana and Andhra Pradesh	98	1.2	168	99	19	7	0	0	0	0	391
Karnataka	60	1.0	91	55	11	0	1	0	0	0	158
Gujarat	45	0.7	77	45	0	0	0	0	0	0	167
Madhya Pradesh	3	—	6	2	1	0	0	0	0	0	9
Uttar Pradesh	4	—	8	0	0	0	0	0	0	0	8
Delhi-NCR	14	—	28	14	6	0	0	0	0	0	48
Puducherry	9	7.2	18	2	1	0	0	0	0	0	30
Chandigarh	39	37.0	69	25	1	0	2	0	0	0	97
Rajasthan	7	0.1	14	7	1	0	0	0	0	0	22
Total	570	*0.5	1,007	510	110	37	4	2	4	1	1,675

ODR, organ donation rate; pmp, people per million population.

*The above mentioned factors should be considered before diagnosing a patient brain dead, as all of them can mimic the clinical picture of brain death.

Source: Shroff S, Navin S. Tier two cities—new kid on the block in the deceased donation transplantation programme as it reaches new heights in India. Editorial. Indian Transplant Newsletter. 2015;15(46):1–3, with permission.

Progressive Ischemic Phase

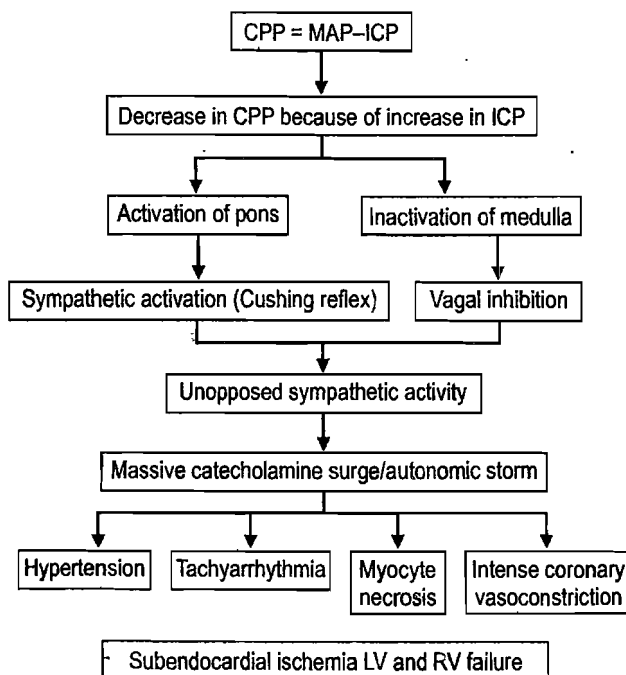
This phase is characterized by rising ICP leading to impaired cerebral perfusion necessitating a compensatory rise in mean arterial pressure (Cushing reflex). Due to pontine sympathetic stimulation, there may be hypertension, tachycardia, and features of acute myocardial dysfunction. A cardiomyopathy-like pattern due to catecholamine-mediated myocyte necrosis and intense coronary vasoconstriction first described by Takotsubo may be seen. This phenomenon against the background of increased oxygen demands leads to subendocardial ischemia and cardiac dysfunction (Flowchart 1).

Brainstem Death Completion Phase

This phase is characterized by withdrawal of sympathetic stimulation with vasodilatation, hypotension, relative hypovolemia, and reduced cardiac afterload and preload. This is compounded by further fluid loss due to associated diabetes insipidus from pituitary ischemia and hyperosmolar therapy for managing elevated ICP. This hemodynamic profile is further complicated by associated acidosis, hypoxia, anemia, hypothermia, relative adrenal deficiency, electrolyte abnormalities, and sepsis⁸ (Flowchart 2).

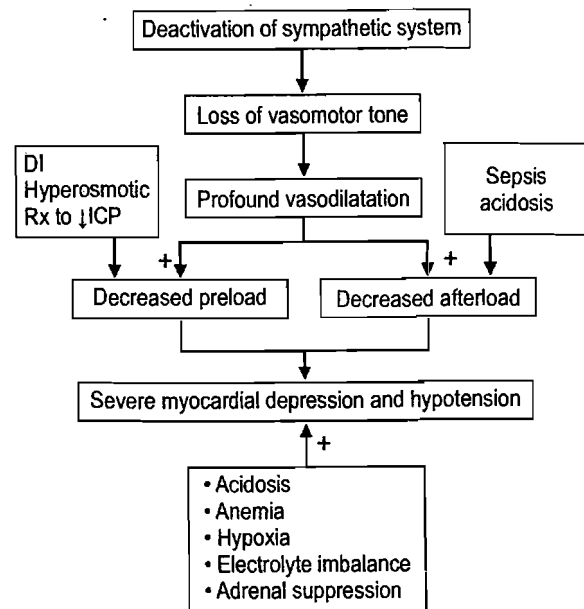
Respiratory System

The primary respiratory center, consisting of the inspiratory and expiratory neurons, is located in medulla oblongata. In brain death, spontaneous respiration does not occur in



CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; LV, left ventricular; RV, right ventricular.

316 **FLOWCHART 1:** Progressive ischemic phase



DI, diabetes insipidus; ↓, decrease; ICP, intracranial pressure; +, aggravates.

FLOWCHART 2: Brainstem death completion phase

patients even when PaCO_2 reaches 55–60 mmHg. Confirming apnea is one of the important aspects of determining brain death. Mechanical stimulation of the carina to induce the cough reflex is useful in detecting residual functioning of the medullary respiratory neurons. Catecholamine surge with increased sympathetic discharges and release of neuropeptide Y causes pulmonary vasoconstriction and increase in pulmonary capillary hydrostatic pressure causing pulmonary edema (neurogenic pulmonary edema). The lungs are also damaged by loss of vasomotor tone, hypotension, and development of systemic inflammatory responses.

Endocrine System

The sella turcica protects the pituitary gland from compression caused by swelling of the brain. The endocrine dysfunction observed in brain death is mainly because of vascular insufficiency caused by increasing ICP. In autopsy studies, posterior pituitary lobe has been found to be preserved in majority and the maximum damage is to the anterior pituitary lobe. Due to axoplasmic disruption, flow of vasopressin from hypothalamus to posterior pituitary is disrupted. Other hypothalamic-releasing hormones were found in trace to subnormal levels.

Temperature Regulation

In brain-dead patients, the neural connection between the temperature-regulating center and peripheral body tissues is lost and the patient becomes poikilothermic. Hence, it is important to maintain body temperature in brain-dead patients to maintain perfusion and avoid acid-base abnormalities. Even during diagnosis of brain death normothermia is one of the important criteria to be fulfilled.

Immune System

Brain death induces a myriad of inflammatory responses which collectively results in systemic inflammatory response syndrome.⁹ The possible mechanisms are:

- Inflammatory mediators released from the ischemic brain
- Catecholamine surge causing:
 - Anaerobic metabolism which results in release of inflammatory mediators
 - Flow-induced shear stress of the endothelial cells
 - Ischemia of the gut
- Neuropeptides released from the nervous system also play a role in inflammation.

MANAGEMENT OF BRAIN-DEAD PATIENT

Once brain death is confirmed, intensivist plays an important role in optimizing the patient. The goals of management shift from improving cerebral perfusion pressure to maintaining hemodynamic stability to maximizing the likelihood of successful organ procurement. It involves multidisciplinary management by collaboration with organ procurement organization (OPO) personnel, preparing the family for devastating news, counseling them on end-of-life issues, and preserving the option of organ donation.

Due to the complex physiological changes, following brain death and its effect on different organs necessitate the importance of multisystem management, which can be described under the following headings.

Monitoring

- Central venous pressure
- Pulmonary artery occlusion pressure: Risks and benefits should be considered, whenever using pulmonary artery catheter
- Invasive arterial blood pressure
- Central venous or mixed venous saturation (SCVO₂ and SVO₂)
- Cardiac output monitoring along with systemic vascular resistance, stroke volume, and cardiac index
- Stroke volume variation or pulse pressure variation
- Transthoracic and transesophageal echocardiography: Echocardiography is usually done for determination of the suitability of the heart for transplantation. Ideally, it should be deferred until the donor has weaned off of catecholamines. If an echocardiography performed early in the course of brain death demonstrates significant cardiac dysfunction, the echocardiography should be repeated 12–24 hours following aggressive donor management
- Arterial blood gases (base deficit and lactate levels)
- Urine output monitoring
- Temperature.

Cardiovascular System

Fluid Management⁶

- Initial intravascular volume replacement with crystalloids
- The preferred isotonic crystalloids are balanced crystalloid and lactated Ringer's solution
- Half normal saline and 5% dextrose solutions are used in the setting of hypernatremia (>155 mEq/dL)
- Hydroxyethyl starch should not be used routinely for resuscitation in organ donors
- Blood and blood products as per requirement to target hemoglobin above 7 g/dL.¹⁰

Vasoactive Drugs

- Catecholamine-induced tachycardia and its harmful effects on heart can be managed by administering esmolol, which increases heart procurement¹¹
- Dopamine considered to be the first line drug for management of cardiovascular collapse following brainstem death because of its immunomodulatory action thereby decreasing the effect of ischemic reperfusion injury^{12–14}
- Vasopressin is an alternative first line agent and can also serve as an additional vasopressor in cases of refractory shock¹⁵
- Norepinephrine is used as an additional pressor when dopamine infusion rates approach more than 10 µg/kg/min or marked hemodynamic instability is present
- Dopamine, dobutamine or epinephrine may be used in primary cardiac pump dysfunction.

Hemodynamic Targets⁷

- Mean arterial pressure at least 60 mmHg
- Central venous pressure around 8–10 mmHg
- Urine output at least 1 mL/kg/h
- Left ventricle ejection fraction at least 45%
- Lowest vasopressor dose possible
- Hemoglobin above 7 g/dL.

Respiratory System

- The focus of pulmonary management is to recruit and retain lung units while limiting tidal volume and inspiratory pressure. This strategy is extrapolated from studies in acute respiratory distress syndrome
- Common approach is a low-tidal volume (6–8 mL/kg), low FiO₂ and relatively high PEEP¹⁶
- Bronchoscopy should be performed in all potential lung donors, both to assess for occult aspiration and infection and to perform therapeutic airway clearance
- Fluid management protocols in lung donor management include aiming for neutral or net negative fluid balance

to avoid volume overload and maintenance of blood pressure with vasopressors rather than aggressive fluid resuscitation.¹⁷

Pulmonary Target

- Partial arterial pressure of O_2/FiO_2 ratio more than 300 mmHg is widely considered the minimum acceptable oxygenation threshold for lung donation.^{6,7}

Endocrine System

Four hormonal resuscitation: Organ Procurement and Transplantation Network and United Nations Network for Organ Sharing multivariate studies on hormonal treatment of brain-dead donors with thyroxine (T3/T4), methylprednisolone, and arginine vasopressin revealed significant increases in the number of organs transplanted and in 1-year survival of kidneys and hearts.¹⁷⁻¹⁹

Vasopressin

- Treatment with antidiuretic hormone should be considered when hypotension persists despite adequate volume resuscitation and also in the presence of diabetes insipidus [as defined by polyuria with urine output >3–4 L/day or 2.5–3.0 mL/kg/h, normal or increased serum osmolality, inappropriately dilute urine (specific gravity <1.005, urine osmolality <200 mOsm/kg water) and hypernatremia ($Na^+ >145$ mmol/L)]
- For the management of circulatory shock, vasopressin at a dose of 0.01–0.04 IU/min is used
- For the management of diabetes insipidus with significant hypernatremia (sodium >145–150 mmol/L) without hypotension desmopressin is used at an intravenous dose of 1–4 µg initially followed by additional dose of 1–2 µg based on the response
- Both vasopressin and desmopressin can be used concurrently in the hemodynamically unstable donor with severe hypernatremia
- Electrolytes should be monitored closely as urinary losses associated with diabetes insipidus can lead to hypokalemia, hypophosphatemia, and hypomagnesemia. These electrolytes should be replenished.

Thyroid Hormone

- Thyroid replacement therapy either alone or as part of a combination hormone therapy with vasopressin, corticosteroids, and insulin should be considered for hemodynamically unstable patients
- Either T3 or T4 can be used, T4 dose is 20 µg bolus and followed by an infusion at 10 µg/h, whereas T3 dose is 4 µg bolus and followed by an infusion at 3 µg/h.⁷

Corticosteroids

- High-dose corticosteroid administration (methylprednisolone 15 mg/kg intravenous bolus followed by 24 hourly or 250 mg intravenous bolus followed by infusion at 100 mg/h) reduces the potential deleterious effects of the inflammatory cascade on donor organ function following brain death²⁰
- Ideally, it should be administered after blood has been collected for tissue typing as it has the potential to suppress human leukocyte antigen expression.

Insulin

- Hyperglycemia in the donor is common and exacerbated by steroid therapy
- Poor glucose control adversely affects donor renal function
- Insulin management should target a glucose level between 120 mg/dL and 180 mg/dL.²¹

Temperature Management

- Donor management should include active warming to maintain a body temperature above 35°C before and during organ procurement.

DONOR CRITERIA

Traditionally, young and healthy brain-dead donors were considered for organ donation. The donor criteria have been extended, though not definitive and evolving, necessitated by a long-waiting list of potential recipients. These extended criteria include advanced age, prolonged cold ischemia time, inferior organ function, and other comorbidities.^{22,23}

Extended Criteria for Heart Donation^{7,24}

- The donor criteria may be extended to 55 years with acceptable recipient mortality rate
- Mild left ventricular hypertrophy (wall thickness <1.4 cm) is acceptable for cardiac transplant
- Prolonged cardiac arrest with return of spontaneous circulation within 20 minutes may be acceptable as a donor criteria.

Extended Criteria for Kidney Donation²⁵

- Donors more than 60 years of age
- Donors 50–59 years of age with two of the following three characteristics:
 1. History of hypertension
 2. Death caused by cerebrovascular accident
 3. Preterminal serum creatinine level more than 1.5 mg/dL.

Extended Criteria for Liver Donation^{26,27}

- Most factors by themselves do not contraindicate liver transplantation. Because of liberalized liver donor selection criteria, all potential donors should be discussed with the local OPO before making any decisions about donor suitability, successful transplantation has been routinely completed with these "marginal" organs
- Livers with a macrovesicular steatosis more than 30% should be approached with caution, weighing the risks and benefits for the intended recipients.

Extended Criteria for Lung Donation²⁸

- Ideal lung donation criteria are over restrictive for donation. As many transplant programs now utilize more liberal criteria, all potential donors should be discussed with the OPO and lung transplant teams to determine suitability for lung donation
- Ideal lung donor criteria:
 - Age less than 55 years
 - Smoking history less than 20 pack-years
 - Clear chest radiograph
 - PaO₂ more than 300 mmHg with 100% FiO₂ and PEEP of 5 cmH₂O
 - Absence of significant chest trauma
 - No evidence of aspiration or sepsis
 - No prior cardiothoracic surgery
 - No organisms on donor Gram stain
 - No purulent secretions or gastric contents on bronchoscopy
 - No history of significant chronic lung disease.

CONCLUSION

Organ donation is the most "sacred gift" that a person can give. It is not only life saving but also life transforming act. Indian statistics of organ donation are not exciting due to the lack of awareness among general public as well as medical fraternity working in peripheries. Both intensivist and primary physician have to play active role in diagnosing and managing brain dead organ donors. Most importantly all emerging intensivists should be trained on brain dead organ management during their academic curriculum.

REFERENCES

1. Wijdicks EFM, Vatek PN, Gronseth GS, et al. Evidence-based guideline update: determining brain death in adults—report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(23):1911-8.
2. Health Resources and Services Administration. (2015). Organ Procurement and Transplantation Network. [online] Available from: <http://optn.transplant.hrsa.gov/>. [Accessed September, 2016].
3. Amalorpavanathan J, Shroff S, Karunakaran CE, et al. (2013). Annual Report from Tamil Nadu Organ Sharing Registry for the year 2013-2014. [online] Available from: <http://www.tnos.org/pdf/report.pdf>. [Accessed September, 2016].
4. Gómez MP, Arredondo E, Pérez G, Manyalich M. International Registry in Organ Donation and Transplantation 2010. *Transplant Proc*. 2012;44(6):1592-7.
5. Johnson RJ, Bradbury LL, Martin K, et al. UK transplant registry. Organ donation and transplantation in the UK—the last decade: A report from the UK national transplant registry. *Transplantation*. 2014;97(Suppl 1):S1-27.
6. Koltoff RM, Blosser S, Fulda GJ, Malinoski D, Ahya VN, Angel L, et al. Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. *Crit Care Med*. 2015;43(6):1291-325.
7. Miller RD, Eriksson LI, Fleisher LA, et al. *Miller's anesthesia*. 8th ed. Philadelphia: Elsevier Health Sciences; 2014.
8. Wood KE, Becker BN, McCartney JG, et al. Care of the potential organ donor. *N Engl J Med*. 2004;351(26):2730-9.
9. Barklin A. Systemic inflammation in the brain-dead organ donor. *Acta Anaesthesiol Scand*. 2009;53(4):425-35.
10. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-17.
11. Audibert G, Charpentier C, Seguin-Devaux C, et al. Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation*. 2006;82(8):1031-6.
12. Kumar L. Brain death and care of the organ donor. *J Anaesthesiol Clin Pharmacol*. 2016;32(2):146-52.
13. Hoeger S, Gottmann U, Liu Z, et al. Dopamine treatment in brain-dead rats mediates anti-inflammatory effects: The role of hemodynamic stabilization and D-receptor stimulation. *Transpl Int*. 2007;20(9):790-9.
14. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: A randomized controlled trial. *JAMA*. 2009;302(10):1067-75.
15. Pennefather SH, Bullock RE, Mantle D, et al. Use of low dose arginine vasopressin to support brain-dead organ donors. *Transplantation*. 1995;59(1):58-62.
16. Mascia L, Päsaro D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA*. 2010;304(23):2620-7.
17. Dare AJ, Bartlett AS, Fraser JF. Critical care of the potential organ donor. *Curr Neurol Neurosci Rep*. 2012;12(4):456-65.
18. Malinoski DJ, Daly MC, Patel MS, et al. Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. *J Trauma*. 2011;71(4):990-5.
19. Novitzky D, Cooper DK, Rosendale JD, et al. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation*. 2006;82(11):1396-401.
20. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: A prospective randomized controlled trial. *Ann Surg*. 2008;248(6):1042-50.
21. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-97.
22. Cameron A, Busuttill RW. AASLD/ILTS transplant course: is there an extended donor suitable for everyone? *Liver Transpl*. 2005;11(Suppl 2):S2-5.
23. Fernandez-Lorente L, Riera L, Bestard O, Carrera M, Gomà M, Porta N, et al. Long-term results of biopsy-guided selection and allocation of kidneys from older donors in older recipients. *Am J Transplant*. 2012;12(10):2781-8.
24. Khasati NH, Machaal A, Barnard J, et al. Donor heart selection: the outcome of "unacceptable" donors. *J Cardiothorac Surg*. 2007;2:13.
25. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation*. 2002;74(9):1281-6.
26. Daga D, Frutos MA, Sella G, et al. Expanded donor criteria due to age: an effort rewarded. *Transplant Proc*. 2006;38(8):2374-5.
27. Renz JF, Kin C, Kinkhabwala M, et al. Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation. *Ann Surg*. 2005;242(4):556-63.
28. Van Raemdonck D, Neyrinck A, Verleden GM, et al. Lung donor selection and management. *Proc Am Thorac Soc*. 2009;6(1):28-38.

Section 7

Hematology/Imaging/ Metabolic

SECTION EDITOR: SHRIKANTH SRINIVASAN

Lung Ultrasound in Intensive Care Unit: Current Application

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INTRODUCTION

Until recently, the use of lung ultrasound (US) as a diagnostic tool was considered impossible on the grounds of conventional knowledge that the US beam cannot normally pass through air-filled structures and as lungs are filled with air, they are not amenable to US imaging.

This theory has been rejected and lung US is currently considered the fastest, noninvasive, diagnostic approach in the intensive care unit (ICU), emergency, and even field settings.¹ In fact, there has been a paradigm shift and lung US is no longer simply restricted to diagnosis—it has become a respiratory monitoring tool.

Lung US is based on the fact that every acute disease reduces lung aeration, changing the lung surface and generating distinct and predictable patterns; this allows for the diagnosis of various conditions and the monitoring of therapeutic interventions.^{2,3}

The main advantage of lung US is that it is a dynamic bedside-scanning tool. The lung US findings complement physical examination findings and clinical impression.⁴ Portable-sonographic equipment also allows US evaluation at any time and in any place and repeated scans can be done to follow up of pathology and have real time monitoring of response to therapy. Besides this, it also has a small learning curve; these features have led to the proliferation in use of lung US by nonspecialists, including emergency room physicians, intensivists and pulmonologists.⁴

In contrast to computed tomography (CT) scans, US is noninvasive and does not employ radiation or contrast material and may be applied on patients, irrespective of their age, during pregnancy, under conditions of renal failure, or in patients with allergy against contrast material.

Lung ultrasonography is superior to standard supine radiography and similar to chest CT in detecting many findings that are important to the intensivist. It is able to detect lung consolidation, alveolar-interstitial fluid accumulation, normal aeration pattern, pneumothorax (PTX) and pleural

Box 1: Current and potential application of lung ultrasound

- Diagnosis of pneumothorax
- Diagnosis of interstitial syndrome
- Diagnosis and differentiation of underlying cause of pleural effusion and selecting the optimal puncture site for pleural tapping
- Diagnosis of pulmonary consolidation and pneumonia
- Diagnosis of atelectasis
- Diagnosis of pulmonary edema and differentiate it from acute respiratory distress syndrome
- Diagnosis of pulmonary embolism
- Monitoring of lung disease (severity, progress and response to therapy)
- Optimizing mechanical ventilation

fluid. The current uses and potential applications are summarized in box 1. The aim of this chapter is to provide an introduction to US imaging of the lungs and to summarize the findings associated with basic respiratory disorders.

PHYSICS OF LUNG ULTRASONOGRAPHY

Due to the large difference in acoustic impedance (resistance to passage of US beams) between air and tissue, there is reflection of the US wave at any tissue-air interface. In addition, air has an unfavorable attenuation coefficient (characterizes how easily air can be penetrated by light, sound, or other energy).

These issues block any attempt to scan through air to deeper body structures and instead produce homogeneous amorphous, gray-white artifacts that occupy the US screen beyond any tissue-air interface. As lung parenchyma is normally filled with air, the lung is not visible as a discrete structural entity with US. However, when air is displaced from the lung by a disease process, US findings change in a predictable fashion, which can be detected and followed up in real time.

Thus, the findings of lung US relate to the ratio of air to fluid within the lung; different artifacts are produced in different conditions proportionate to the degree of aeration/deaeration. Lung US is based on a systematic analysis of these artifacts. For example, edematous lung, though still aerated, has air artifact patterns that are different than normally aerated lung. Likewise, lung that is consolidated from pneumonia or atelectasis (i.e., airless) appears as a well-defined hyperechoic structure.

While aerated lung will block US visualization of an abnormality deep within the lung, most lung processes that are of interest to the intensivist (e.g., pneumonia and hydrostatic pulmonary edema) have US findings that extend to the periphery of the lung and can easily be visualized and interpreted.⁵

HOW TO PERFORM LUNG ULTRASONOGRAPHY?

Unlike chest radiography or chest CT where the radiologist and intensivist interpret a static image, lung US relies on dynamic image acquisition performed by the intensivist at the bedside of the critically ill patient.

Machine and Transducer

Lung ultrasonography may be performed with practically any US machine with 2-dimensional (2D) scanning capability. Some newer machines have image-smoothing technology, which filters out artifacts by default, such machines may not be appropriate for lung imaging. Doppler capability is not required for critical care lung ultrasonography.

Transducer Selection

Since lung US depends on interpretation of artifacts, any transducer—linear, curvilinear, phased array, or microconvex

probe can be used. It is suggested to start the scan using a curvilinear probe, which allows us to scan two to three interspaces in one go, especially, when we wish to scan the chest rapidly and for posterior sections of the chest wherein the chest wall is thicker. For a detailed assessment and procedural guidance, the linear transducer may be selected.

One must be flexible in approach to scan areas of interest and change of transducers may be required. High-frequency linear transducers (9–12 MHz) best visualize the pleura, its anatomy and lung sliding; lower frequency curvilinear transducers (2.5–5 MHz) allow better appreciation of the extension of B-lines and of consolidations/effusions. When evaluating findings such as A-lines or B-lines (see later), the depth setting on the machine should be set to image deeper structures. When examining for sliding lung, the depth setting should be set for imaging near structures.

Initially, the transducer is positioned in a longitudinal orientation and perpendicular to the skin with its marker directed to the head of the patient and perpendicular to the ribs. By moving the transducer along a series of longitudinal scan lines while imaging through adjacent interspaces, the examiner can perform a complete lung examination in an efficient manner while constructing a three-dimensional image of the thorax. In case, there is a finding suggestive of pathology, the transducer can then be rotated and oriented transversely between the ribs to view specific intercostal spaces in details so that the extent of the pathology can be defined.

It is helpful to examine the thorax using an organized section approach, so that results can be referenced to a particular area.

In general, patients are examined in the supine position, with the head of the bed elevated. The anterior and posterior axillary lines are the reference points for the examination, dividing the thorax into three zones, which are further subdivided into upper and lower sections by a line passing through the nipple (Fig. 1).

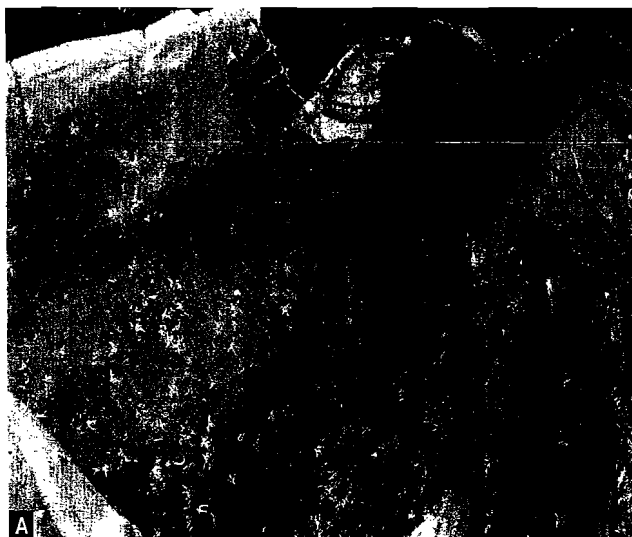


FIG. 1: Ultrasound zones of thorax

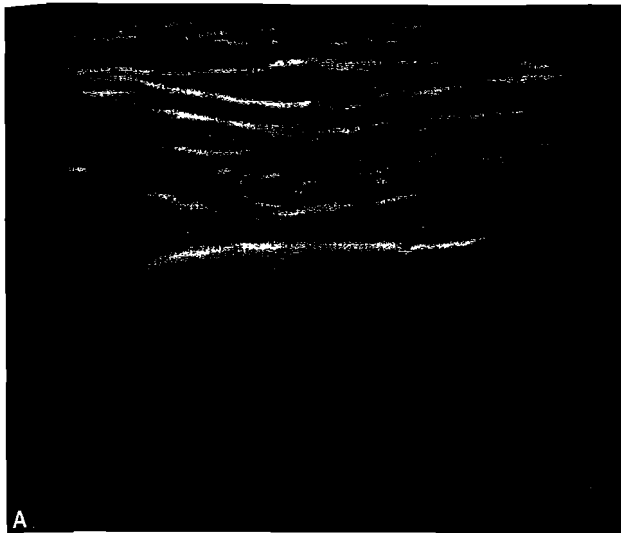


FIG. 2: Pleural line

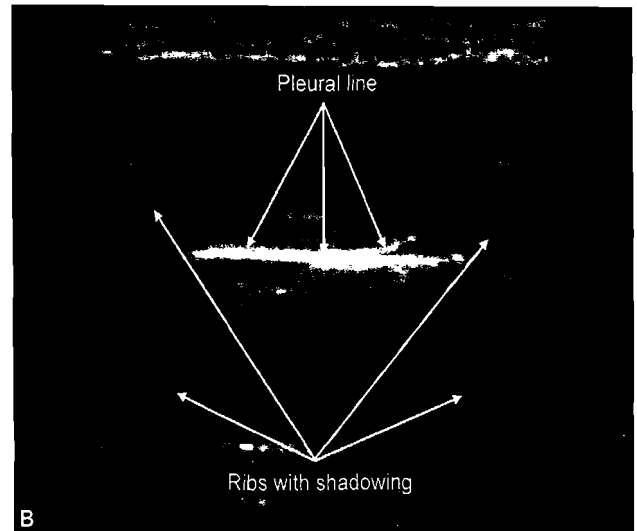
The anterior zone is bordered by the sternum and the anterior axillary line, while the lateral zone lies between the anterior and posterior axillary lines. The posterior region lies behind the posterior axillary line. This is frequently an important area to image, as pleural effusions and posterior consolidations are found in the dependent thorax. To image these areas, the transducer may have to be pressed into the patient's mattress and angled toward the center of the body. In order to completely examine the posterior lung in the supine patient, the patient may be placed in the lateral decubitus position. As with the anterior and lateral examination, lung ultrasonography is then performed by applying the transducer at multiple interspaces on the back. These divisions do not correlate to any specific lobe of the lung and serve to ensure a systematic sectorial approach to examination.

IMPORTANT FINDINGS OF LUNG ULTRASONOGRAPHY

The important findings of critical care lung ultrasonography are as follows.

Pleural Line

With the transducer held perpendicular to the skin surface in a longitudinal orientation and centered over an intercostal space, the depth has to be adjusted to examine the pleural interface. One can see the images of the skin subcutaneous tissues and muscles. The intercostal space is bordered by the hyperechoic surface of ribs and underlying rib shadows; in the intercostal space, we see a horizontally orientated hyperechoic line approximately 0.5 cm deep to the origin of the rib shadows. This hyperechoic line is an artifactual line, which represents the interface of the visceral and parietal pleural surfaces and is called the pleural line (Fig. 2).



Lung Sliding

Lung sliding is a key lung US finding. During respiration, the two pleural surfaces slide against each other, and this appears as a shimmering white line artifact. This to and fro movement of the pleural line in synchrony with the respiratory movements is called lung sliding.^{1,2}

Lung sliding is easily identified on B-mode US especially being more pronounced in the lateral and lower part of the lungs as it descends down during inspiration.

On M-mode US, lung sliding appears as a specific sign, known as the seashore sign, which is characterized by a linear pattern corresponding to the chest wall (no movement) above the pleural line (light or hyperechoic) and a homogeneous granular pattern an artifact generated by respiratory cycles and air movement below the pleural line (Fig. 3).

Lung sliding is found in normal lungs, and is reduced or absent in pathologies that affect lung mobility, lung sliding becomes restricted in pulmonary overexpansion, acute respiratory distress syndrome (ARDS), chronic adhesions, fibrosis, phrenic palsy, jet ventilation, while it disappears in PTX, complete atelectasis, pleural fibrosis and apnea.⁶ The positive-predictive value of abolished lung sliding is 87% in a general population,⁷ and falls to 56% in the critically ill, and to 27% in patients with respiratory failure.⁸

A-lines

The normal lung parenchyma (as well as any anatomical structure filled with gas) cannot be seen beyond the pleural line, given that the presence of air prevents US wave propagation. When US beams encounter the air tissue interface there is production of artifacts known as A-lines.

A-lines are horizontally orientated lines seen deep to the pleural line. They represent reverberation artifacts from US reflection between the pleural surface and the outer surface of

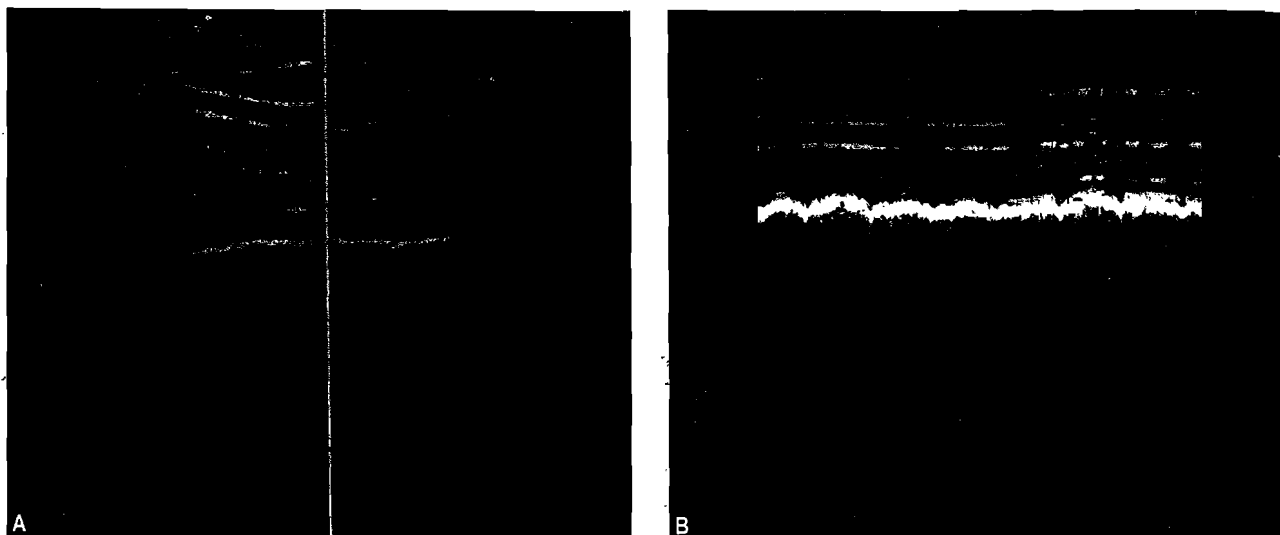


FIG. 3: Lung sliding and seashore sign

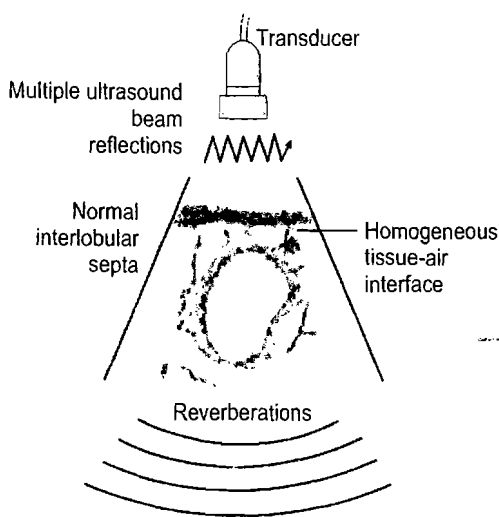


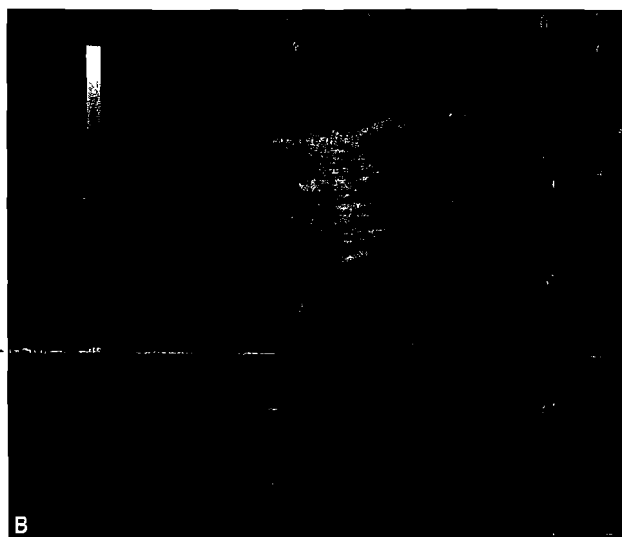
FIG. 4: A-lines

the chest wall. Therefore, their depth is a multiplicative of the distance between the skin surface and the pleural line (Fig. 4).

A-lines denote presence of air, either within the lung as in a normal aerated lung or outside the lung as in a case of PTX. Hence, A-lines with lung sliding are consistent with normal aeration pattern. Only A-lines with no lung sliding could denote a PTX.

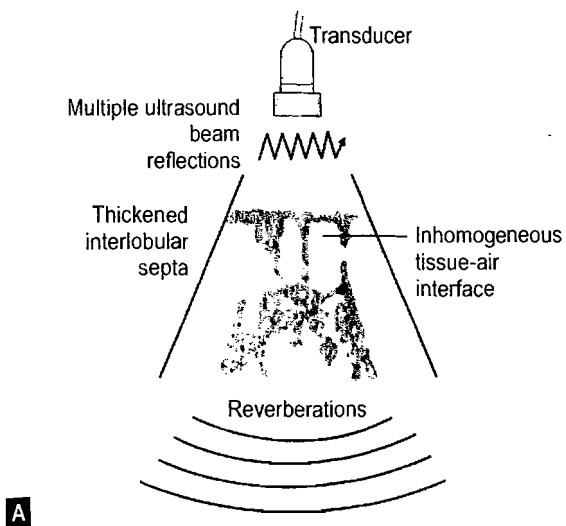
B-lines

B-lines are artifacts that appear as vertically orientated lines that originate at the pleural interface. They must efface A-lines where the two intersect. They always extend in a ray-like fashion to the bottom of the viewing screen, and they generally move synchronously with lung sliding. They may, however, be immobile in the absence of lung sliding.



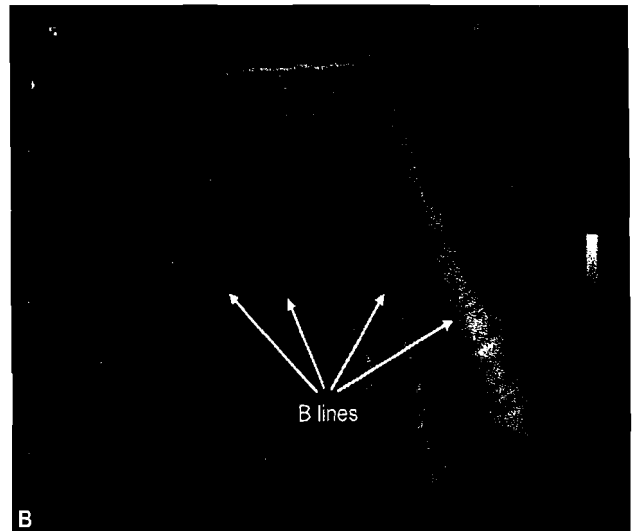
The B-line artifact strongly correlates with interstitial edema.⁹ B-lines are formed when air and water are simultaneously hit by US beams, as occurring when sub-pleural interlobular septa are edematous (Fig. 5). Three or more B-lines in two adjacent intercostal spaces may be considered as significant finding.

The presence of B-lines with a distance <7 mm apart corresponds to interlobular tissue thickening. The pattern of diffuse B-lines in lung parenchyma with a distance less than 3 mm are also called lung rockets corresponds with a ground-glass pattern in chest CT scan¹⁰ (Fig. 6). A positive correlation was found between the number of B-lines (comet score) and pulmonary capillary wedge pressure (PCWP), as well as with extravascular lung water (EVLW).^{11,12} Since B-lines arise from the pleural line, their presence rules out a PTX in that field.²



A

FIG. 5: B-lines: how they are formed?



B

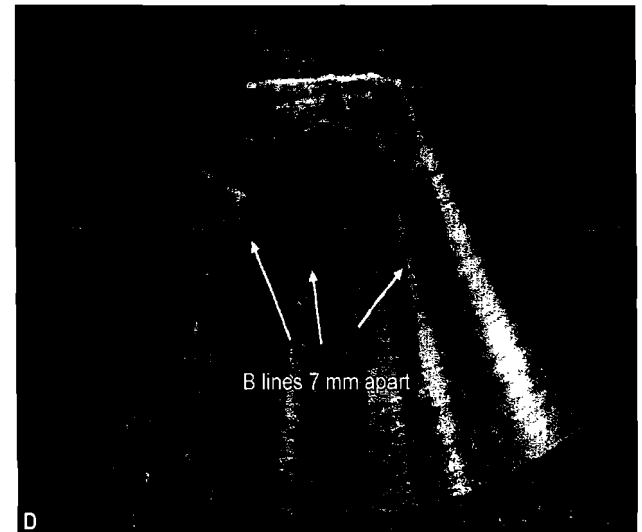
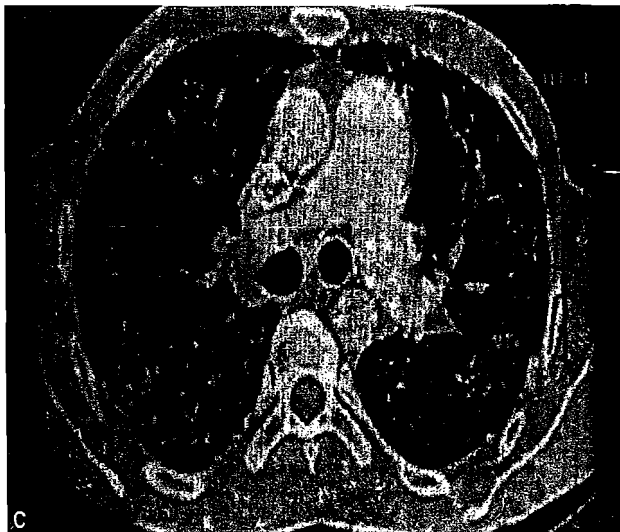
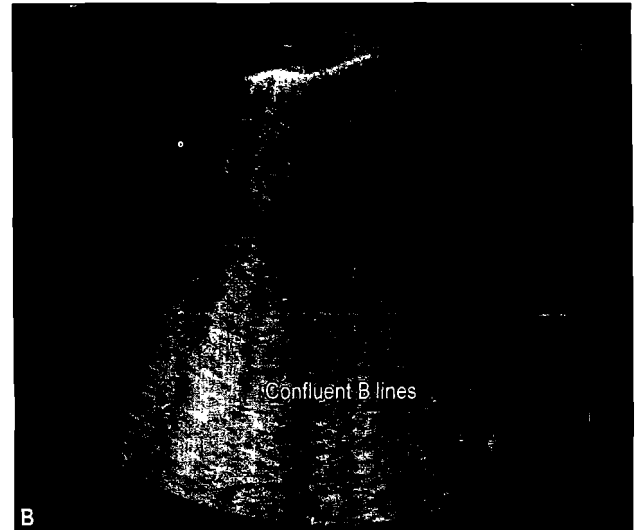
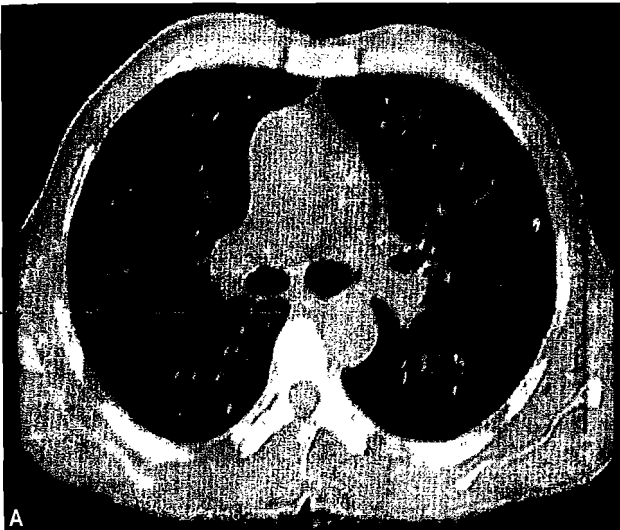


FIG. 6: Computed tomography correlation of B-lines. A and B, Ground glass shadows on computed tomography correlates to confluent B-lines. C and D, Interstitial infiltrates correlates with B-lines 7 mm apart

E-lines

E-lines are formed due to subcutaneous emphysema. Here, the air bubbles infiltrate into the subcutaneous tissues hence, the tissue air interface moves up from the pleural line to the subcutaneous fat and muscle planes. This leads to formation of vertical artifacts similar to B-lines, but emerging at different levels from the subcutaneous tissues and muscle planes (Fig. 7). The clinical significance of the presence of E-lines is that it confirms the presence of subcutaneous emphysema and since the tissue air interphase has moved up the pleural line and underlying lung cannot be visualized and commented upon. Subcutaneous emphysema forms one of the pitfalls in lung US as one cannot comment on the underlying lung in its presence.

Lung Pulse

In addition to lung sliding that occurs synchronous with the respiratory cycle, the pleural line may move in synchrony with cardiac pulsation. This movement, termed lung pulse, is caused by the force of the cardiac pulsation being transmitted to the lung and hence onto the visceral pleura. Like lung sliding, lung pulse indicates that the visceral and parietal pleural surfaces are opposed to each other at the site of transducer application.

The lung pulse is an initial sign of atelectasis, because when there is no appreciable sliding synchronous with breathing and instead the pleural line just pulsates with the heartbeat, this suggests that the underlying lung is static, not collapsed away from the chest wall, but also not involved in gas exchange.

Presence of lung pulse also rules out a PTX in that field because it is produced when the two layer of pleura are opposed to each other allowing the transmitted cardiac pulsations to be visualized.¹³

Consolidation

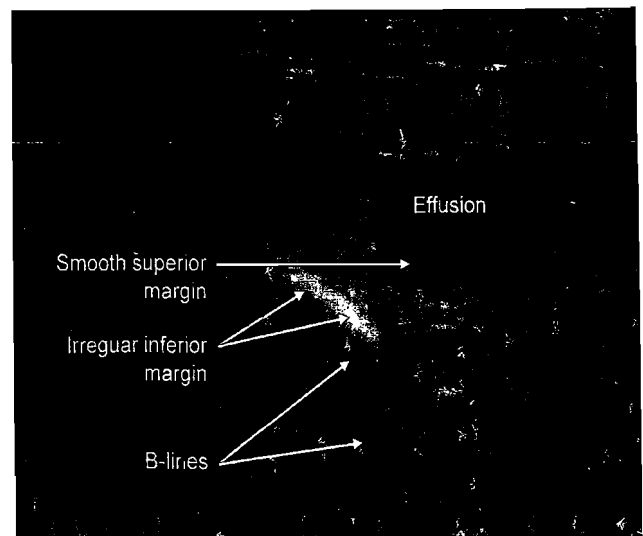
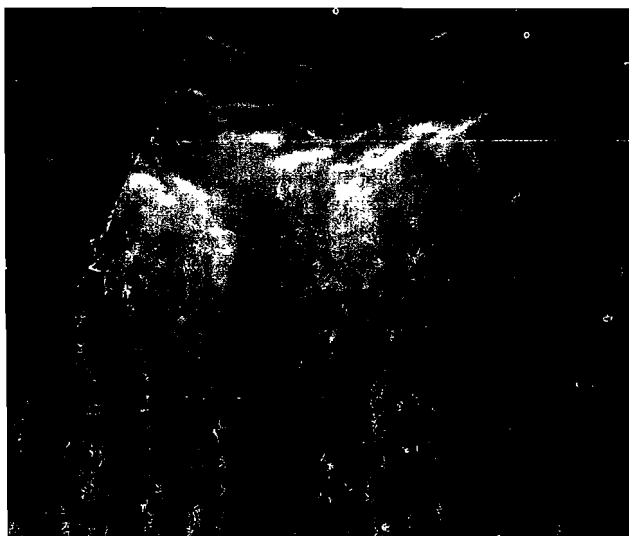
Seven items are required to define alveolar consolidation:

1. Location: Above the diaphragm, in the thorax
2. Pattern: Arising from the pleural line
3. Real image, i.e., not artifactual, as an aerated lung would give
4. Tissue-like pattern resembling liver (hence the term "hepatization")⁶
5. Anatomic boundaries with superficial boundary at the level of the pleural line or the deep boundary of a pleural effusion if present, and a deep boundary usually irregular with the aerated lung (called the shred sign)¹ as seen in nontranslobar consolidation (Fig. 8) or regular in case of whole-lobe involvement (translobar consolidation)
6. Absence of the "sinusoidal sign" for distinguishing alveolar consolidation from potentially associated pleural effusion (see section on pleural effusion)
7. Internal hyperechoic punctiform or linear elements, known as air bronchograms, and intrinsic dynamics of these bronchograms, a pattern called "dynamic air bronchogram".¹⁴

Consolidation index may be used to calculate its size. This is done by calculating the distance between surface and core (from the bottom to the top of the screen) and the longitudinal diameter (from the left to the right of the screen).^{1,14,15} The other way is to measure the maximal thickness of the consolidation area, which can vary from <20 mm (small) to >50 mm (large).^{1,14,15}

Air Bronchogram

Air bronchogram can be seen inside the consolidation as hyperechoic areas and are divided into static and dynamic air bronchogram.



328 FIG. 7: E-lines—subcutaneous emphysema

FIG. 8: Shred sign—translobar consolidation

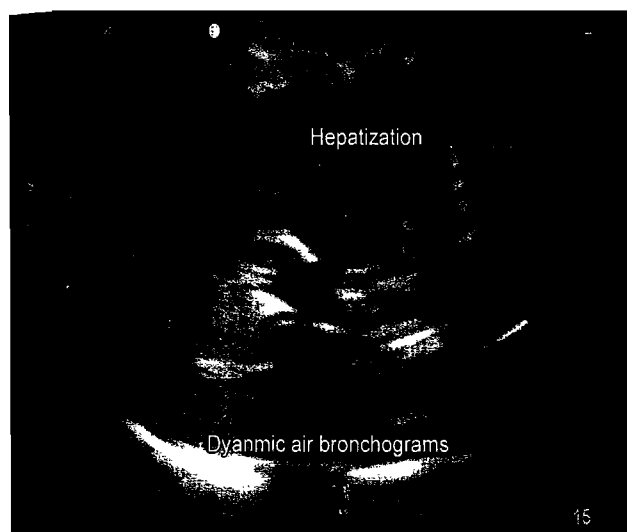


FIG. 9: Hepatization with dynamic air bronchograms

Atelectatic areas have static bronchogram, which is identified by absence of any dynamic movement during respiration. The reason being air is entrapped inside the lung which is not aerated thus creating static artifacts.

Dynamic air bronchogram on the other hand shows hyperechoic areas inside a consolidation, which moves with respiration which signifies patent communication with airways. It is not seen in atelectasis, but it can be seen in 60% of cases of infectious alveolar consolidation^{16,17} (Fig. 9).

Atelectasis

Atelectasis is characterized by the following features:^{1,13,16}

- Change in the imaging location of the heart
- Abolition of the dynamic movement of the diaphragm
- Diaphragm raised by the least 2 cm (in the supine position)
- Presence of a lung pulse
- Absence of dynamic air bronchograms.

Two types of atelectasis are seen: (i) obstructive and (ii) compressive atelectasis.¹⁸

Obstructive atelectasis occurs due to blockade of bronchi by mucus plugs or opposite side endobronchial intubation. They may have: (i) various form and shapes depending on the deaerated area, (ii) no dynamic air bronchogram, (iii) presence of lung pulse, and (iv) small pleural effusion (in comparison to compressive atelectasis).

Compressive atelectasis occurs secondary to large-pleural effusion. It has a typical free floating "waving hand" appearance of lung in a large effusion. There is rapid return to reaeration pattern after re-expansion of lung-following removal of effusion and this can be visualized in real time by US.

BASIS FOR ULTRASOUND SUITABILITY FOR MONITORING LUNG AERATION CHANGES

Ease of use, bedside availability, and repeatability make lung US particularly suited to detect spatial and temporal heterogeneity of lung aeration in patients with respiratory failure and provide key information for their clinical management.

Change in aeration, especially increase in deaeration is readily visualized by lung US. A spectrum of US findings from normally aerated tissue to complete loss of aeration exists, and each different lung US pattern corresponds to a given degree of aeration.¹⁹

Progressive loss of air lung US is sonologically seen as transition from normal A-lines plus lung sliding to the appearance of B-lines, followed by an increase in B-line number and density. This was in turn followed by the appearance of subpleural consolidations, which finally enlarge and deepen, eventually encompassing the entire lung³ (Fig. 10).

The accuracy of lung US in assessing aeration of the lung has been further demonstrated in critically ill patients. A lung

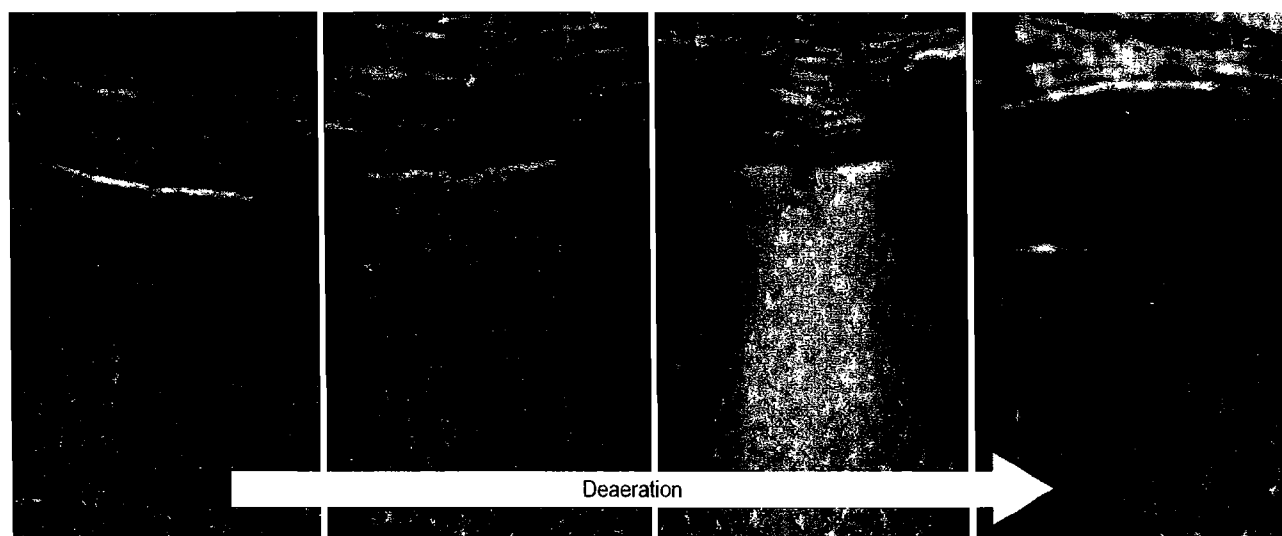


FIG. 10: Ultrasound detection of changes in aeration pattern

US score-quantified aeration changes observed in ventilator-associated pneumonia (VAP) patients upon initiation of antimicrobial therapy show a tight correlation with CT-measurements of lung aeration (day 0 vs day 7).²⁰

The scoring was based on progression or regression of patterns of normality, space B-lines, and/or small subpleural consolidation, coalescent B-lines, and consolidation.

When compared with the pressure-volume curve method for assessing positive end-expiratory pressure (PEEP)-induced lung recruitment in acute lung injury (ALI)/ARDS, the same score was accurate in detecting significant increases in lung aeration (>600 mL, detected by a score ≥ 18). Accuracy diminishes for milder degrees of reaeration (a 75–450 mL increase is associated to a score ≥ 14).²⁰

PATHOLOGICAL CONDITIONS DETECTED BY LUNG ULTRASOUND

Pneumothorax

Diagnosis of PTX requires four steps:

1. Abolished lung sliding: Predominantly found anteriorly in all significant cases in supine patients. It has a 95% sensitivity and 100% negative-predictive value.⁷ Pneumothorax, therefore, is confidently ruled out wherever lung sliding is present.^{7,21}
2. Pneumothorax generates a completely motionless air-tissue interface using real-time. M-mode shows a standardized stratified pattern—the stratosphere sign (Fig. 11)
3. Absence of B-lines in the affected area: Since B-lines emerge from the pleural line, the presence of even a single B-line in the imaged area rules out presence of PTX in that area. The only artifacts that are seen are A-lines
4. Detection of the “lung point”:²² The lung point is found at the site where partially collapsed lung is still opposed to

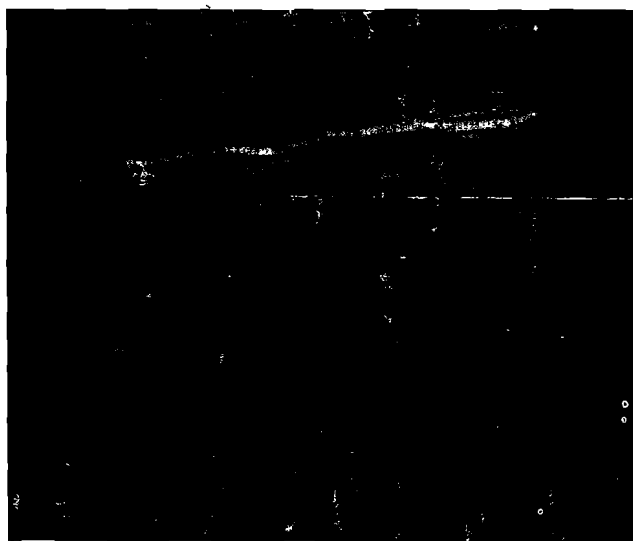


FIG. 11: Pneumothorax: static air-tissue interface with A artifacts

the inside of the chest wall and a part pushed away from the chest wall due to PTX. This appears on US as a zone of transition where there is lung sliding and an abrupt transition to a nonsliding, nonpulsating static A pattern (Fig. 12). The finding of lung point is diagnostic for the presence of PTX. Unfortunately, while 100% specific for PTX, it is relatively insensitive and related to operator experience. The localization of the “lung points” shows good correlation to the extension of PTX on CT.²¹ The more lateral the “lung points” on the chest in supine patients, the larger the air collection. Lung point is absent in case of complete PTX, there may be multiple lung points in traumatic PTX.

Based on the diagnostic accuracy, the amount of time required, the availability, and the costs, US is the diagnostic modality of choice, in particular, if a tension PTX is suspected. The sonographic diagnosis of PTX relies mainly on the loss of respiratory motion of the pleura and B-lines as well as evidence of horizontal artifacts (A-lines). However, because these criteria are nonspecific, a comparison with the contralateral lung is strongly recommended. Ultrasound is also useful in confirming lung re-expansion following drainage.

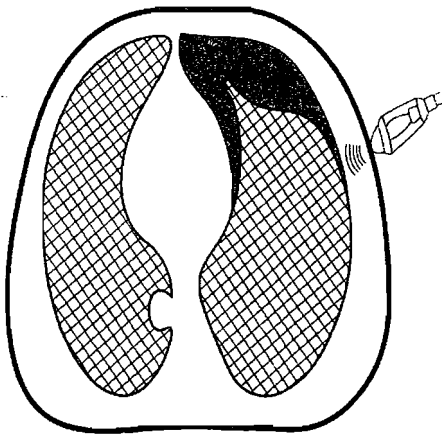
Alveolar-interstitial Syndrome

It is characterized by presence of a B-profile consisting of more than three B-lines on a longitudinal-scanning plane. B-lines became closer and confluent as the degree of lung wetness and deaeration increases. Alveolar-interstitial syndrome includes pulmonary edema, interstitial lung disorders and ARDS. Lung US can distinguish anterior interstitial (spread apart B-lines 7 mm apart) from posterior alveolar patterns (confluent B lines), which is a challenge for anteroposterior radiography.

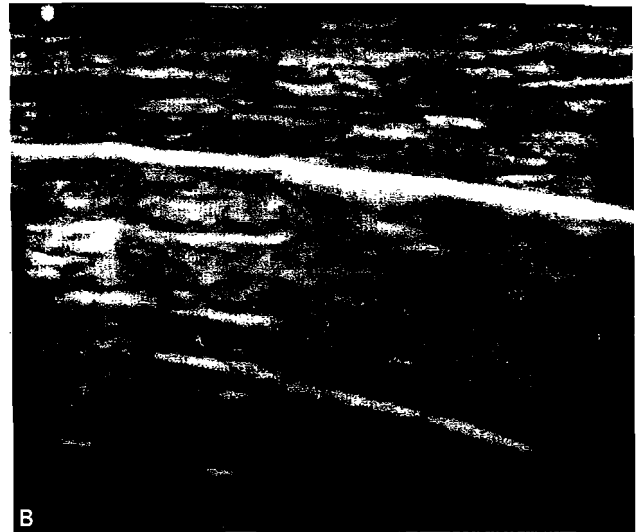
Pulmonary Edema, Acute Lung Injury, and Acute Respiratory Distress Syndrome

Pulmonary edema typically manifests with B-lines that initially prefer the lung bases but with increasing capillary venous pressure that extend to the medium and superior fields. These findings are usually bilaterally and symmetrical. Furthermore, pleural line abnormalities are rarely observed in cardiogenic pulmonary edema.

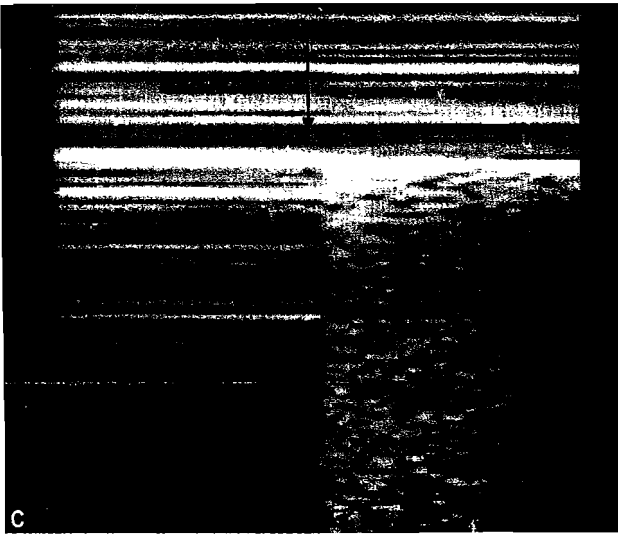
In contrast, patients with ALI/ARDS, B-lines have a nonhomogeneous distribution with evidence of spared areas and are constantly associated with important pleural line abnormalities: irregular-fragmented pleural line and presence of subpleural consolidations.^{8,18} Thus, considering the high sensitivity and specificity of US, this can be the first modality for distinguishing pulmonary edema from ALI/ARDS (Fig. 13).



A

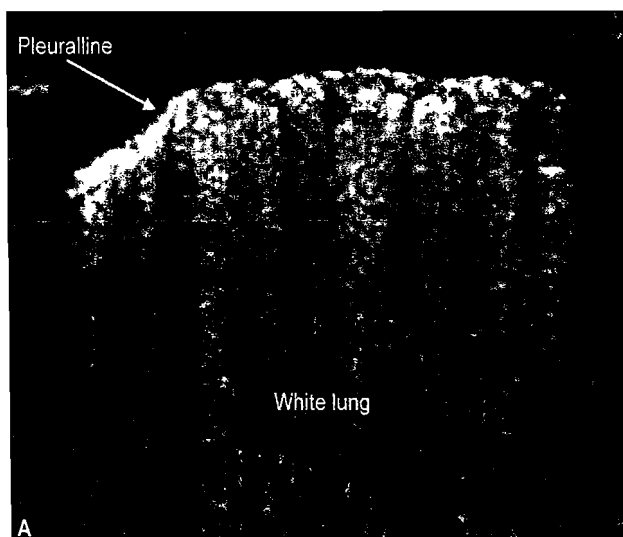


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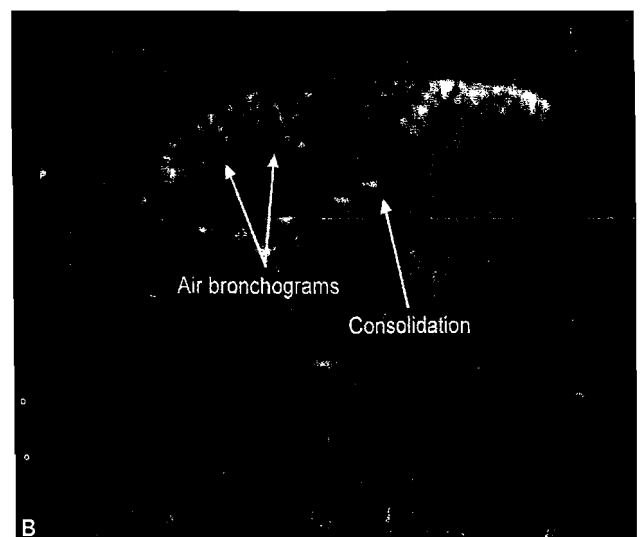


C

FIG 12: Lung point. **A and B,** Zone of transition between aerated (sliding) lung and lung collapsed away by pneumothorax. **C,** M-mode C showing stratosphere sign and transition to seashore sign



A



B

FIG. 13: **A,** Acute pulmonary edema with thickened pleural line and confluent B-lines (white lung). **B,** Acute respiratory distress syndrome with fragmented pleural line and subpleural consolidations

Lung Contusion

Approximately one-fifth of the patients with blunt chest trauma suffer from lung contusion, localized within the traumatic thoracic region.²³ Whereas radiograph of the lung may be inconclusive, sonographic detection of these signs strongly indicates lung contusion. Lung contusion may be suspected on finding one of the following features:¹⁸

- Localized alveolar-interstitial syndrome
- Lacking of a large-focal effusion
- Subpleural, hypoechoic and irregular-bordered lesions without air-inlets
- Margins of constant dimension even during breathing.²⁴

A lung contusion indicated by means of US must be strictly monitored as the condition is known to worsen in the days following the diagnosis often leading to the development of ALI/ARDS.²⁴

Pulmonary Embolism²⁵

In patients with acute respiratory failure, the combination of predominant anterior bilateral A-lines (hyperechoic, roughly horizontal lines and arising at regular intervals from the pleural line reflecting a regular lung surface) plus evidence of venous thrombosis showed a sensitivity of 81%, a specificity of 99% and a positive/negative predictive value of 94%/98%, respectively, for diagnosing pulmonary embolism (PE).⁸

Pleural Effusion

Pleural effusion is a common problem in critically ill patients. Ultrasound is more sensitive than clinical examination and chest X-rays for the diagnosis of pleural effusion. The sensitivity and specificity of lung US for identifying pleural effusion were 90% and 73%, respectively. It is especially effective in the differential diagnosis between effusions and pulmonary atelectasis.^{6,26,27}

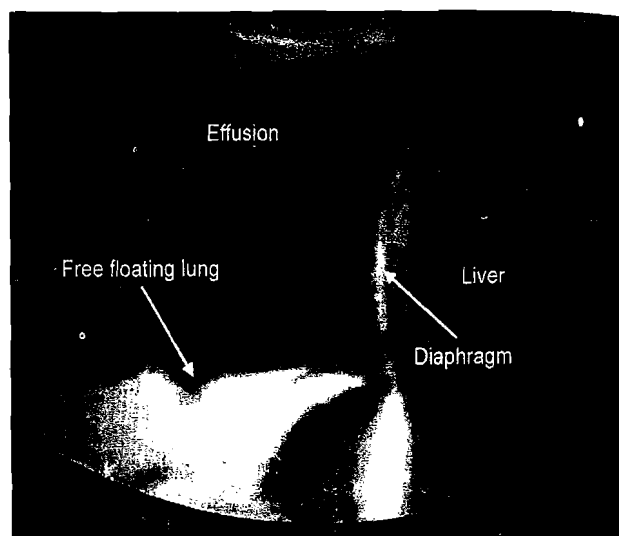


FIG. 14: Pleural effusion seen as anechoic collection with relevant landmarks including chest wall, diaphragm, liver, floating lung

Pleural effusion appears as dark (hypoechoic) and homogeneous image in the dependent regions of the lung.

For an adequate evaluation of pleural effusion, it is necessary to identify three findings:

1. Anatomical boundaries chest wall, lung, diaphragm, and adjacent solid organs (liver/ spleen) confirming the intrathoracic location of the collection, especially if a thoracentesis has been planned (Fig. 14)
2. Anechoic space—the pleural effusion itself
3. Dynamic changes: Intermittent lung aeration, compressed lung or both (atelectasis); diaphragmatic movement; and sinusoidal inspiratory movement.

Two sonographic signs are associated with pleural effusions: (i) the quad sign and (ii) the sinusoid sign.²⁸

The quad sign is a static-sonographic sign observed in pleural effusion. It consists of four lines representing the pleural, rib, fluid and lung. The anechoic space enclosed by these four lines represents the pleural effusion (Fig. 15).

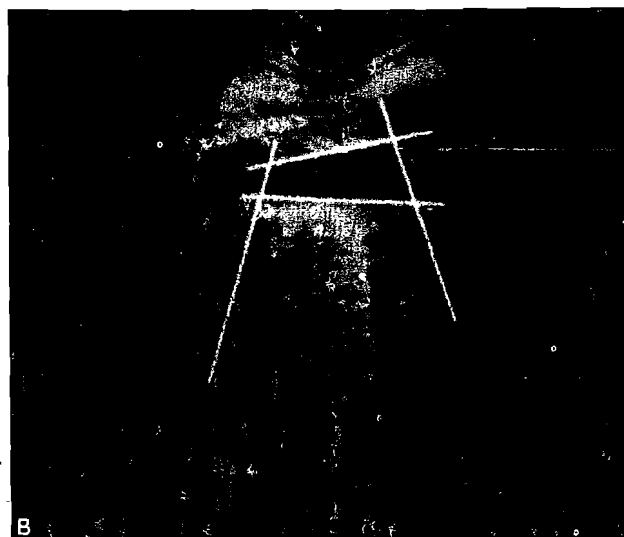
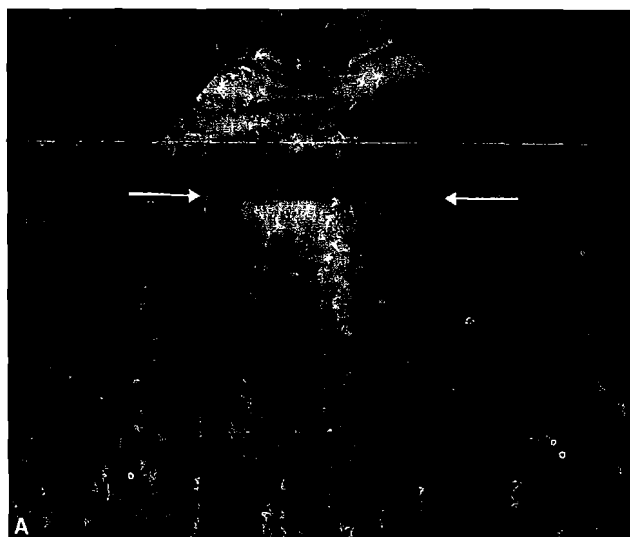


FIG. 15: Quad sign: anechoic pleural effusion bordered by four imaginary lines—two along both rib shadows, one beneath chest wall and one on surface of lung pushed away by effusion

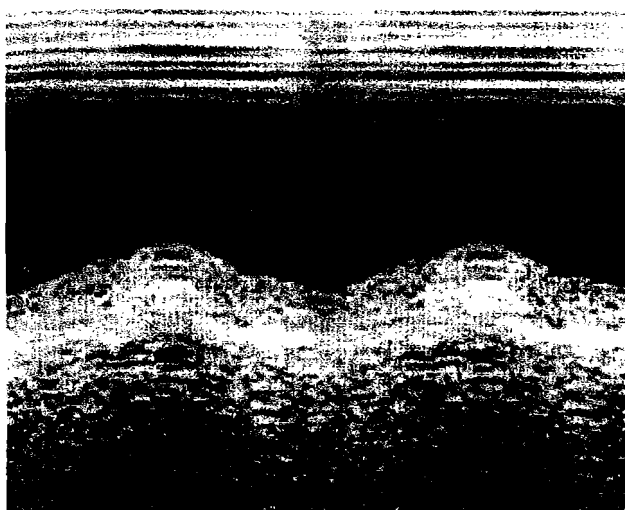


FIG. 16: Sinusoid sign: movement seen on M-mode as the lung floats toward and away from probe with inhalation and exhalation

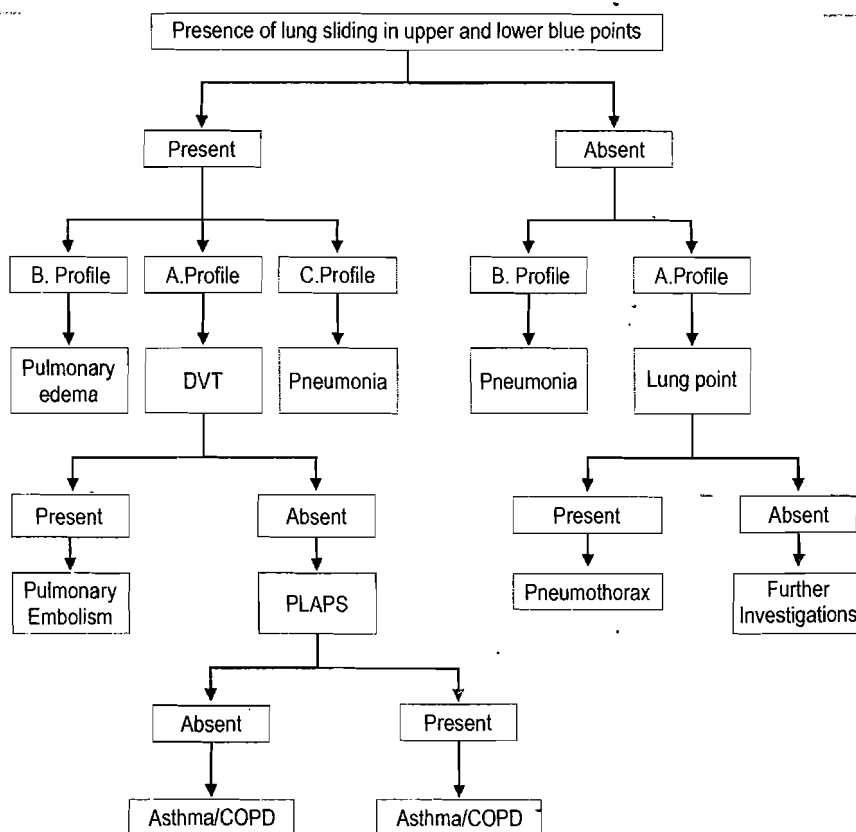
Sinusoid sign is a dynamic sonographic sign in M-mode describing the movement of the lung floating toward and away from the chest wall with every inhalation and exhalation, which is displayed as sinusoidal pattern. Similar to the quad sign, this sign has a high sensitivity and specificity for pleural effusion. It helps to differentiate effusion from a

solid hepatized lung and also indicates possibility of using small needle for withdrawing fluid (Fig. 16).

DIFFERENTIAL DIAGNOSIS OF RESPIRATORY FAILURE

Lung US allows a standardized evaluation of patients with dyspnea based on the profile of lung US findings, together with screening for leg-vein thrombosis. This approach, designated the bedside lung ultrasound in emergency (BLUE) protocol,⁸ can provide immediate answers to situations in emergency situations. The BLUE protocol divides lung US findings into distinct profiles (Flowchart 1).

Presence of lung sliding with A-lines signifies a normal lung pattern, which in acute respiratory failure could be due to severe bronchospasm or pulmonary emboli. A screening US of leg to exclude venous thrombosis is helpful to identify patients with PE. The absence of lung sliding, along with the presence of A-lines, is highly predictive of PTX, which can be further confirmed by identifying the lung point. If there are areas with no lung sliding and predominant B-lines, this will point toward presence of anterior consolidation in which case there may be asymmetric findings between the hemithoraces. A normal pattern associated with the presence of pleural effusion and posterior consolidation may also be noted.



Note: Note: This decision tree does not aim at providing the diagnosis. It indicates a way for reaching a 90.5% accuracy when using lung ultrasound. PLAPS (posterior/lateral alveolar and/or pleural syndrome): Presence of consolidation and/or effusion in the lateral and posterior parts of the lung.

FLOWCHART 1: Bedside lung ultrasound in emergency protocol; COPPD, chronic obstructive pulmonary disease

Source: Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest*. 2008;134:117-25.

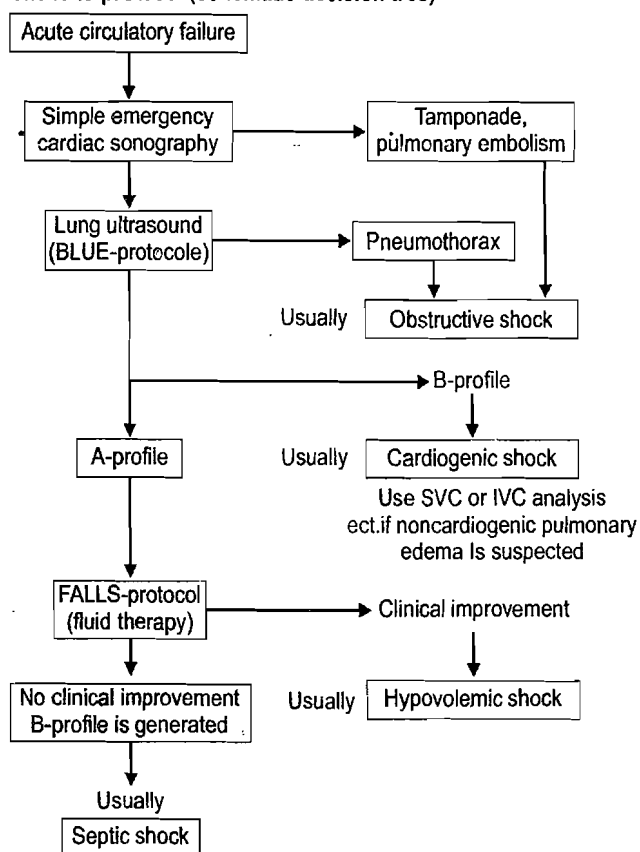
FLUID ADMINISTRATION LIMITED BY LUNG SONOGRAPHY²⁹

Overt accumulation of interalveolar fluid manifested clinically by pulmonary edema is usually preceded by accumulation of fluid in the pulmonary interstitium and subpleural interlobular septa, which may be clinically silent but accessible to US. When the amount of this fluid overtakes the reabsorption capacity of lymphatics overt alveolar edema ensues.

A-predominance profile in lung US is a criterion for lung tolerance to fluid therapy. If a B-predominance replaces an A-predominance following fluid therapy, this indicates recent interstitial syndrome (i.e., the likelihood of acute pulmonary edema) suggesting thereby limit of fluid therapy.

During fluid resuscitation in hypovolemic or distributive shock one should aim to correct clinical features of shock while maintaining A-profile signifying dry lung. In cardiogenic shock, on the other hand B-profile characteristic of wet lung is usually presents on admission (Flowchart 2).

The falls-protocol (schematic decision tree)



BLUE, bedside lung ultrasound in emergency; FALLS, fluid administration limited by lung sonography; SVC, superior vena cava; IVC, inferior vena cava.

FLOWCHART 2: Fluid administration limited by lung sonography protocol (schematic decision tree)

DIAPHRAGMATIC FUNCTION

Lung US can be useful in the evaluation of diaphragmatic function, through the evaluation of diaphragmatic movement on M-mode during a deep inhalation, as well as through tidal volume and the sniff test. The curvilinear probe is selected for visualizing the diaphragm on both sides (between the midclavicular and anterior axillary line) using the liver and spleen as windows. Diaphragmatic palsy is detected by paradoxical movement on M-mode trace.

LUNG-RELATED PROCEDURES AND THEIR MONITORING

A wide range of bedside procedures performed on critical respiratory disease patients benefit from information provided by lung imaging.

Monitoring the Response to Interventions

The response to clinical interventions can be monitored by lung US. A study evaluating patients with renal failure and pulmonary congestion demonstrated that the reduction in the number of B-lines was proportional to the reduction in the volume of EVLW, which was accompanied by clinical improvement of the patients.

To Predict and View Real-time Lung Recruitment

Lung US has the potential to predict lung recruitability based on observations of lung morphology, which is a key predictor of the response to recruitment manoeuvres.³⁰ Diffuse deaeration is associated with a more homogeneous interstitial pattern characterized by coalescent B-lines more present in dependent areas is more amenable to recruitment. On the other hand, early stage-focused distribution of aeration loss (a state associated with poor recruitability and major risks of overdistention of aerated regions) is represented by a nearly normal lung US pattern or a paucity of B-lines in anterolateral areas and consolidation or crowding of B-lines in dorsal ones.

However, hyperinflation cannot be accurately diagnosed with lung US, even if one observes markedly reduced sliding in the context of a normal lung US pattern. Lung US findings cannot be used in isolation to determine appropriate PEEP.

To Decide on Ventilator Strategy

Along with the overall clinical picture, lung US can support the choice of pronation (if dorsal consolidations prevail) and monitor its effects in real time.³¹ Very empirically, but effectively, detection of derecruited areas even in less severe contexts than ARDS allows optimization of ventilatory

strategy, for example, by means of postural therapy, or in the choice of using noninvasive ventilation rather than continuous positive airway pressure in spontaneously breathing patients.

Aid in Bronchoscopy

By helping the intensivist recognize the atelectatic nature of a consolidated area (absence of a “dynamic air bronchogram” or presence of “fluid bronchogram”, positive-predictive value 94%),¹⁶ lung US can suggest the need to restore bronchus patency by means of fiberoptic bronchoscopy. When a distal airway specimens indicated by the suspicion of pneumonia, lung US can identify the best lobe to target, with higher accuracy than chest X-ray.

Management of Pleural Effusions

The decision to perform pleural drainage is based on estimating the potential compressive effect of the effusion, which depends on the volume of the effusion. Lung US can estimate pleural effusion volume semiquantitatively (an expiratory interpleural distance at the thoracic base >45–50 mm or >50 mm accurately predicts >500 mL³² or 800 mL³³ effusions, respectively) or quantitatively (multiplane approach, based on the effusion length times midheight area formula).³⁴ These estimates tightly correlate with CT-scan estimates and collected fluid volumes. The procedure itself is optimized by identifying the most dependent and safest site of puncture²⁸ and by monitoring the results of the thoracentesis in real-time.

Furthermore, lung US has shown superiority to standard chest X-ray and CT-scan in characterizing the internal complexity of an effusion—detection of complex septated or complex nonseptated effusions (internal echoes and mobile particles), as in hemothorax/empyema, can suggest the use of chest tube drainage. Ultrasound-aided management of pleural effusions in febrile ICU patients also hastens diagnosis and aggressive treatment of empyema.³⁵

Assessment of Weaning from Mechanical Ventilation

Lung US has been shown to be useful in monitoring and managing the weaning process from mechanical ventilation.

- It allows for detection and treatment of obstructive atelectasis, derecruited areas and relevant effusions so as to optimize the starting conditions for extubation and spontaneous breathing trials (SBTs)
- Lung US provides information that can be used to potentially predict the success or failure of a SBT. By multisite quantification with a lung US four-tiered score (0 = normal pattern; 1 = multiple spaced B-lines; 2 = multiple coalescent B-lines; 3 = consolidation), the

state of lung aeration before the SBT and the amount of derecruitment after the trial can be described. Higher scores are detected in patients more likely to subsequently develop postextubation respiratory distress.³⁶ The lung US score at the end of an SBT predicts postextubation distress with an area under the receiver-operating characteristic (ROC) curve of 0.86, 95% confidence interval (CI) (0.79–0.93), with 0.82 sensitivity and 0.79 specificity for a lung US score more than 14, a better performance than plasma B-type natriuretic peptide values and echocardiographic-derived parameters. A lung US score at end SBT of ≤ 12 or more than 17 accurately identifies patients with a low or high likelihood of postextubation distress, respectively

- As an accurate tool for the differential diagnosis of cardiogenic and obstructive causes of respiratory failure, lung US may also allow prompt recognition of a cardiogenic component of acute postextubation respiratory distress
- Finally, diaphragm ultrasonography, easily obtained during lung US scanning of lower quadrants, provides additional insights on tolerance to weaning. One could identify patients at high risk of difficulty weaning during an SBT (M-mode measure diaphragmatic descent <10 mm correlates with higher rates of primary, 83% vs. 59% $p = 0.01$, and secondary weaning failure, 50% vs. 22% $p = 0.01$).³⁷ Furthermore, a cutoff value for spleen and liver downward displacement of >11 mm can predict successful extubation (84.4% and 82.6% sensitivity and specificity respectively, better than traditional weaning parameters).³⁸

LIMITATIONS OF ULTRASOUND

In general, pulmonary lesions can only be detected by US under the following conditions:

- The location of pulmonary lesion is peripheral and extends up to the pleura: Precise quantification of the extension of lung lesions and deeper lesions without consolidation/effusion is not possible
- Absence of air in the pleural space (no PTX)
- Absence of subcutaneous accumulation of air (no subcutaneous emphysema)
- The lesion is not hidden behind a bony structure: Ribs or scapula

Other limitations include:

- Inability to visualize lung when there are hindrances to probe placement like wound/dressings, defibrillator pads, extensive tissue edema or very obese patients
- Appropriate standardized training is crucial, at this time, the systematic use of lung US in ICUs is still scarce
- It cannot evaluate hyperinflation, a relevant issue in ALI/ARDS patient's management
- Infection transmission via the US probe also deserves attention and further investigation.

CONCLUSION

Lung US has the potential to become a reference tool for bedside dynamic respiratory monitoring in the ICU and can fill the image-resolution gap between chest radiographs and CT scans. It is noninvasive, easily repeatable, and provides rapid and accurate evaluation of the respiratory status. It minimizes radiation exposure to medical personnel. Continued research is needed to place lung US in evidenced-based diagnostic imaging strategies and implement it into goal-directed diagnosis and monitoring. Standardized training and a systematic use should be advocated to fully utilize its potential.

REFERENCES

- Lichtenstein D. Should lung ultrasonography be more widely used in the assessment of acute respiratory disease? *Expert Rev Respir Med*. 2010;4:533-8.
- Mayo PH. Ultrasound evaluation of the lung. In: Levitov A, Mayo PH, Stonim AD, (Eds). *Critical Care Ultrasonography*. New York: McGraw-Hill; 2009. Pp. 251-8.
- Via G, Lichtenstein D, Mojoli F, et al. Whole lung lavage: a unique model for ultrasound assessment of lung aeration changes. *Intensive Care Med*. 2010;36:999-1007.
- Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest*. 2011;140:1332-41.
- Bolliger CT, Herth FJF, Mayo PH, et al. *Clinical Chest Ultrasound: From the ICU to the Bronchoscopy Suite*. Progress in Respiratory Research, Vol 37. Basel: Karger; 2009. pp. 76-81.
- Anantham D, Ernst A. Ultrasonography. In: Mason RJ, Broaddus VC, Murray JF, Nadel JA (Eds). *Murray and Nadel's textbook of respiratory medicine*. 5th ed. Philadelphia: Saunders-Elsevier; 2010. Pp. 445-60.
- Lichtenstein D, Menu Y. A bedside ultrasound sign ruling out pneumothorax in the critically ill: lung sliding. *Chest*. 1995;108:1345-8.
- Lichtenstein D, Mezière G. Relevance of lung ultrasound in the diagnosis of acute respiratory failure. The BLUE-protocol. *Chest*. 2008;134:117-25.
- Lichtenstein D, Mezière G, Biderman P, et al. The comet-tail artifact: an ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med*. 1997;156:1640-6.
- Bouhemad B, Zhang M, Lu Q, Rouby JJ. Clinical review: Bedside lung ultrasound in critical care practice. *Crit Care*. 2007;11:205.
- Gargani L. Lung ultrasound: a new tool for the cardiologist. *Cardiovasc Ultrasound*. 2011;9:6.
- Frassi F, Gargani L, Gligorova S, et al. Clinical and echocardiographic determinants of ultrasound lung comets. *Eur J Echocardiogr*. 2007;8:474-9.
- Lichtenstein DA, Lascols N, Prin S, et al. The "lung pulse": an early ultrasound sign of complete atelectasis. *Intensive Care Med*. 2003;29:2187-92.
- Lichtenstein D, Lascols N, Mezière G, Gepner A. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med*. 2004;30:276-81.
- Gehmacher O. Ultrasound pictures of pneumonia. Review paper. *Eur J Ultrasound*. 1996;3:161-7.
- Lichtenstein DA, Mezière G. Ultrasound diagnosis of atelectasis. *Intensive Care*. 2005;12:88-93.
- Lichtenstein D, Mezière G, Seitz G. Le broncogramme aériendynamique, unisigne échographique de consolidation alvéolaire non retractile. *Reanimation*. 2002;11:98.
- Reissig A, Copetti R, Kroegel C. Current role of emergency ultrasound of the chest. *Crit Care Med*. 2011;39:839-45.
- Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;38:577-91.
- Bouhemad B, Liu ZH, Arbelot C, et al. Ultrasound assessment of antibiotic-induced pulmonary reabsorption in ventilator-associated pneumonia. *Crit Care Med*. 2010;38:84-92.
- Dulchavsky SA, Hamilton DR, Diebel LN, et al. Thoracic ultrasound diagnosis of pneumothorax. *J Trauma*. 1999;47:970-1.
- Lichtenstein D, Mezière G, Biderman P, Gepner A. The lung point: an ultrasound sign specific to pneumothorax. *Intensive Care Med*. 2000;26:1434-40.
- Wustner A, Gehmacher O, Hammerle S, et al. Ultrasound diagnosis in blunt thoracic trauma. *Ultraschall Med*. 2005;26:285-90.
- Rocco M, Carbone I, Morelli A, et al. Diagnostic accuracy of bedside ultrasonography in the ICU: feasibility of detecting pulmonary effusion and lung contusion in patients on respiratory support after severe blunt thoracic trauma. *Acta Anaesthesiol Scand*. 2008;52:776-84.
- Mathis G, Blank W, Reissig A, et al. Thoracic ultrasound for diagnosing pulmonary embolism: A prospective multicenter study of 352 patients. *Chest*. 2005;128:1531-53.
- Diacon AH, Brutsche MH, Soler M. Accuracy of pleural puncture sites: a prospective comparison of clinical examination with ultrasound. *Chest*. 2003;123:436-41.
- Zanobetti M, Poggioni C, Pini R. Can chest ultrasonography replace standard chest radiography for evaluation of acute dyspnea in the ED? *Chest*. 2011;139:1140-7.
- Lichtenstein D, Hulot JS, Rabiller A, et al. Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. *Intensive Care Med*. 1999;25:955-8.
- Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest*. 2015;147:1659-70.
- Constantin JM, Grasso S, Chanques G, et al. Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. *Crit Care Med*. 2010;38:1108-17.
- Tsubo T, Yatsu Y, Tanabe T, et al. Evaluation of density area in dorsal lung region during prone position using transesophageal echocardiography. *Crit Care Med*. 2004;32:83-7.
- Vignon P, Chastagner C, Berkane V, et al. Quantitative assessment of pleural effusion in critically ill patients by means of ultrasonography. *Crit Care Med*. 2005;33:1757-63.
- Roch A, Bojan M, Michelet P, et al. Usefulness of ultrasonography in predicting pleural effusions >500 mL in patients receiving mechanical ventilation. *Chest*. 2005;127:224-32.
- Remerand F, Dellamonica J, Mao Z, et al. Multiplane ultrasound approach to quantify pleural effusion at the bedside. *Intensive Care Med*. 2010;36:656-64.
- Tu CY, Hsu WH, Hsia TC, et al. Pleural effusions in febrile medical ICU patients: chest ultrasound study. *Chest*. 2004;126:1274-80.
- Soummer A, Perbet S, Brisson H, et al. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress. *Critical Care Med*. 2012;40:2064-72.
- Kim WY, Suh HJ, Hong SB, et al. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med*. 2011;39:2627-30.
- Jiang JR, Tsai TH, Jerng JS, et al. Ultrasonographic evaluation of liver/spleen movements and extubation outcome. *Chest*. 2004;126:179-85.

Metrics of Glucose Control in the Intensive Care Unit

Sunil Karanth

INTRODUCTION

Hyperglycemia is a common metabolic abnormality encountered in many animal species during periods of stress. This evolutionary highly preserved response concurs with the old adage that "hyperglycemia is a compensatory response that provides fuel to vital organs". Numerous studies¹ have reported a high incidence of hyperglycemia in critically ill patients, with a recent Australian study in a single medical-surgical intensive care unit (ICU) revealing at least 80% of patients developed hyperglycemia in the first 48 hours after ICU admission (defined as a fasting blood sugar >126 mg/dL or random blood sugar >200 mg/dL).² Though the epidemiological association between hyperglycemia and higher mortality and morbidity in different disease states³⁻⁵ is well-documented, discrepancy exists in randomized controlled trials (RCTs)⁶⁻¹⁰ regarding the intensity of blood sugar control and improved clinical outcomes. The metrics of glucose control in the ICU is made even more complex by factors such as superimposed risk of hypoglycemia, glucose variability, appropriate subgroup of patients, method of achieving glucose control, and the preexisting glycemic milieu of each patient.^{11,12} Thus, the level at which this stress response becomes a maladaptation has been a matter of debate for over a decade.

BIOLOGY OF HYPERGLYCEMIA DURING CRITICAL ILLNESS

Glycemia, in the critically ill, has a complex interaction with nutrition, patient factors, and cellular derangements. Hyperglycemia is often induced in the critically ill by a state of insulin resistance. This insulin resistance is created by counterregulatory hormones (catecholamines, glucagon and cortisol) and elevated levels of cytokines [interleukin (IL)-1, IL-2 and tumor necrosis factor- α (TNF- α)]. This results in impaired peripheral uptake of glucose and increased endogenous production of glucose (gluconeogenesis and

glycogenolysis), and associated with depletion of glycogen stores in the fasting state.¹³⁻¹⁵ Though hyperglycemia can promote inflammation, it has several potential deleterious effects like increasing production of anti-inflammatory cytokines (like IL-10), impaired neutrophilic function, decreased intracellular bactericidal activity, decreased opsonic activity, and decreased innate immunity.^{15,16} Mitochondria function is damaged by various mechanisms including oxidative stress. Repair and regeneration of mitochondria is hampered by hyperglycemia, which could predispose to cellular failure and consequent multisystem organ failure.¹⁷

Immobilization in ICU is associated with numerous problems. One of them is the reduction in exercise-stimulated glucose uptake. Some early data confirms this finding in clinical care with evidence of increased glucose transport¹⁸ and reduced daily insulin requirements¹⁹ in patients undergoing early mobilization in the ICU.

There exists a complex relationship between enteral feeding and hyperglycemia. In normal physiology, ingestion of an enteral meal triggers a complex enterohumoral response. This response causes a release of numerous hormones needed to regulate intestinal motility, nutrient absorption, as well as gall bladder and pancreatic islet cell function. After a bolus meal a pulsatile increase in the insulin secretion is triggered, which is dampened by continuous tube feeding. Furthermore, in animal models there is evidence to suggest a greater insulin resistance with continuous feeds in comparison to intermittent feeds.^{20,21} Further research is needed to validate this point. Acute hyperglycemia itself would be one of the risk factors for development of ileus.²²

RANDOMIZED STUDIES FOR GLYCEMIC CONTROL IN INTENSIVE CARE UNIT

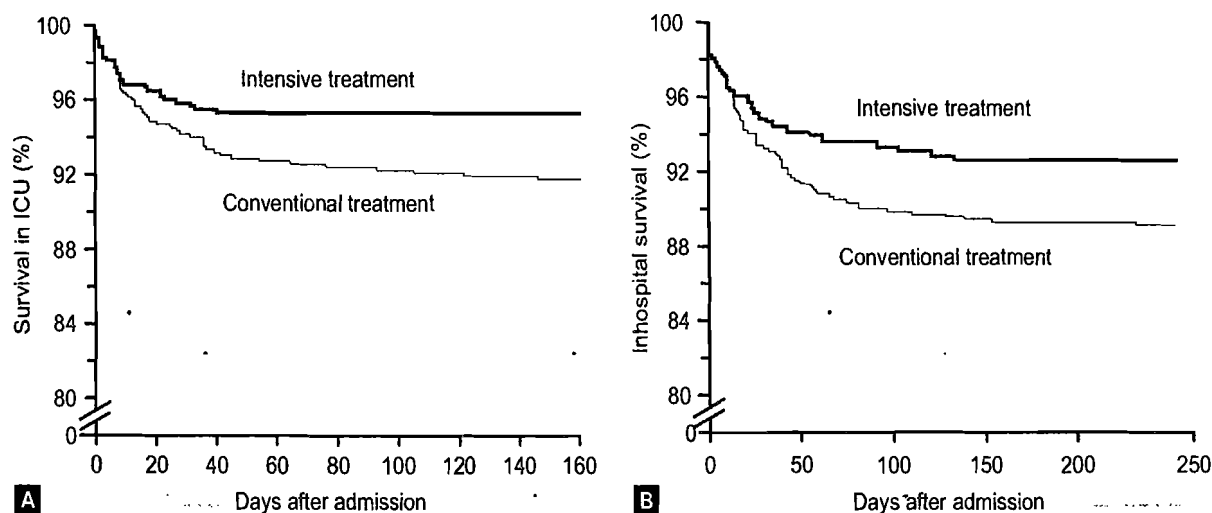
The era of glycemic control in the ICU started with the first RCT in this subject by van den Bergh et al. in 2001.⁶ In a

single-center study—postoperative cardiac surgical unit, comparison of intensive insulin therapy (RBS 80–110 mg/dL) with conventional insulin therapy (RBS 180–200 mg/dL) was performed by the authors. A statistically significant reduction in mortality (Fig. 1) was noted in patients on intensive insulin therapy (4.6 vs. 8%) with further amplification in the result for patients requiring ICU care for more than 5 days. This outcome difference was especially pronounced in patients with a septic focus. Significant improvement was also noted in secondary outcomes as well.

Publication of this paper in 2001, created a water-shed period in therapeutic management of septic patients. This was one of the few preventive interventions known to improve

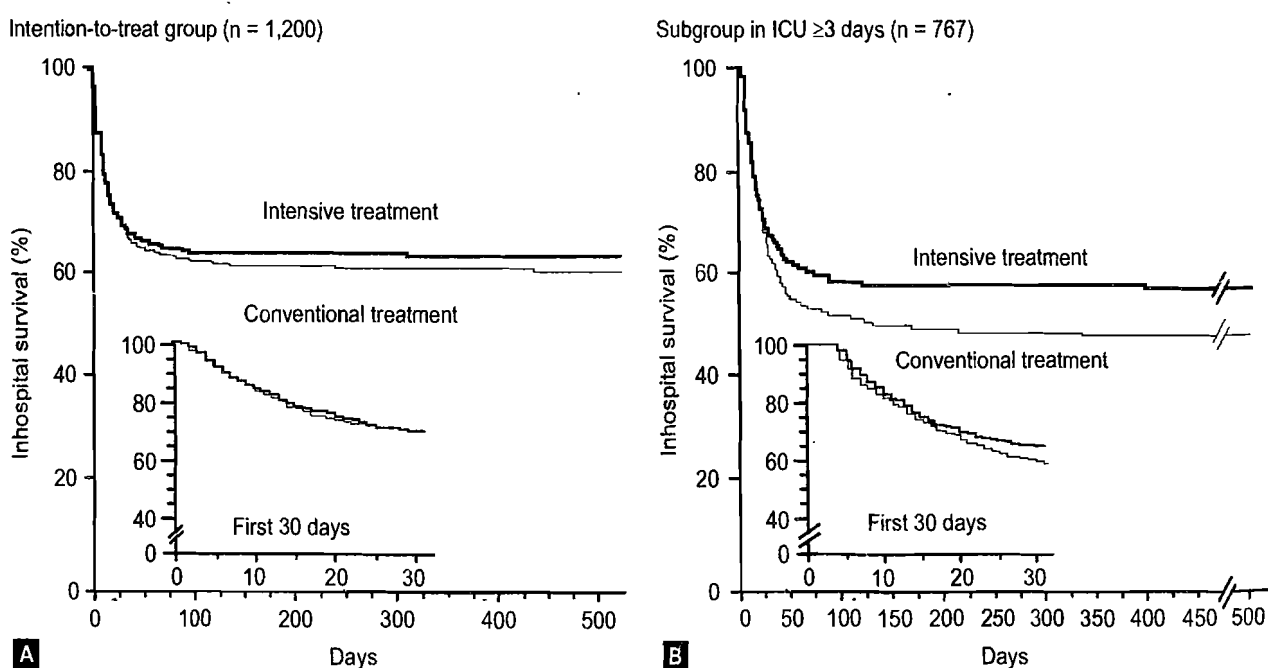
mortality in ICU. However, a number of flaws existed with this RCT like single center, not blinded, high-glucose challenge in the controls, high mortality in the controls, and the presence of predominantly postoperative cardiac surgical patients.

However, subsequent studies including one from the same authors on predominantly medical patients, failed to show such a large difference in mortality. Van den Berghe et al. performed a RCT comparing medical patients randomized to intensive and conventional therapy.⁷ They found no significant change in in-hospital, ICU or 90-day mortality. However, a subgroup analysis of all patients in the ICU staying for greater than 3 days was noted to have a statistically significant difference in mortality (Fig. 2).



ICU, intensive care unit.

FIG. 1: Kaplan-Meier curves showing cumulative survival of patients who received intensive insulin treatment or conventional treatment in the intensive care unit (ICU). Patients discharged alive from A, the ICU and B, the hospital were considered to have survived. In both cases, the differences between the treatment groups were significant⁶



ICU, intensive care unit.

FIG. 2: Kaplan-Meier curves for A, in-hospital survival for all medical patients and B, patients staying over 3 days in the intensive care unit⁷

However, a statistically significant reduction was noted in development of new acute kidney injury and earlier weaning from the ventilator.

A subsequent meta-analysis of the two studies from the same authors, revealed a statistically significant reduction in mortality without any detectable harm.²³ The benefit seemed to be present mainly in patients staying in ICU more than 3 days, while for patients admitted for less than 3 days, no potential harm was noted.³ However, this benefit did not seem to be present for patients with a past history of diabetes mellitus.

Further multicentric studies were conducted by other groups with less pronounced difference in mortality with intensive insulin therapy. Even more concerning was the increased risk of serious adverse effects like hypoglycemia in patients receiving intensive insulin therapy.

Brunkhorst et al.⁸ conducted a multicentric RCT in 18 German ICUs among critically ill patients with severe sepsis. The trial had a 2 × 2 factorial design to compare the effect of intensive insulin therapy versus conventional insulin therapy and synthetic colloid versus Ringer lactate for resuscitation. The study was stopped half way for safety reasons as the incidence of severe hypoglycemia was significantly higher in the intensive insulin group (17 vs. 4.1%, $p < 0.001$), with no change in 28-day mortality (Fig. 3).

Similar results were obtained from a multicentric European trial in a mixed medical-surgical critically ill population, with no difference in mortality, but increased risk of severe hypoglycemia with intensive insulin therapy (8.7 vs. 2.7%).¹⁰

The death knell for intensive insulin therapy was finally dealt by the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial. This was a multicentric RCT with over 6,000 critically ill patients conducted across Australia, New Zealand,

and North America. Patients who were expected to stay for 3 or more days in the ICU were randomized to intensive insulin therapy (81–108 mg/dL) as against conventional glucose target with a glucose less than 180 mg/dL. This target was chosen for the control arm, in view of data suggestive that a blood sugar of less than 180 mg/dL was the expected standard of practice in Australia, New Zealand and parts of Canada during that time. This study revealed that intensive glycemic control was associated with a higher mortality in comparison to a moderate glycemic control of less than 180 mg/dL.⁹ The intensive glycemic control group had a mortality of 27.5% as against a mortality of 24.9% in the conventional group with an odds ratio of 1.14 for the intensive group ($p < 0.02$). A total of patients developed severe hypoglycemia in the intensive glycemic control group as against 0.5% in the conventional group.

More recently in a meta-analysis by Griesdale et al., a pooled analysis of data²³ from different studies, including the NICE-SUGAR trial, revealed no difference in outcomes with the use of intensive glycemic control.²⁴

Thus, the pendulum on the metrics of glycemic control has swung from poor glycemic control, to tight glycemic control, in the last one decade and now back to a neutral position of moderate glycemic control in critically ill. Following analyses of all the RCTs and meta-analyses, the present recommendation is to maintain the blood sugar in the range of 140–180 mg/dL. There is very strong data to suggest that a blood sugar of more than 180 mg/dL is associated with worst outcomes, while values below 140 mg/dL are associated with a higher risk of severe hypoglycemia.

PRACTICAL AND COMPREHENSIVE MANAGEMENT TO GLYCEMIC CONTROL IN INTENSIVE CARE UNIT

Target Population

As deduced by the RCTs and meta-analyses, a moderate blood sugar control of 140–180 mg/dL seems optimal. However, a policy of “one size fits all” may not be appropriate to all critically ill patients.

Van den Berghe et al.⁷ in their second RCT involving critically ill medical patients found that presence of pre-existing diabetes mellitus had no change in outcome with intensive glycemic control. The reason for the same was unclear, but possibility of compensatory mechanisms in place to protect against cellular injury from acute hyperglycemia cannot be ruled out. In a large retrospective analysis of over 44,000 patients across nine ICUs, Krinsley et al. found no change in mortality with increasing blood sugar levels in diabetic patients, while nondiabetics showed worse outcomes with worsening hyperglycemia²⁵ (Fig. 4).

Multiple observational studies have shown that in neurologically injured patients, even moderate hyperglycemia

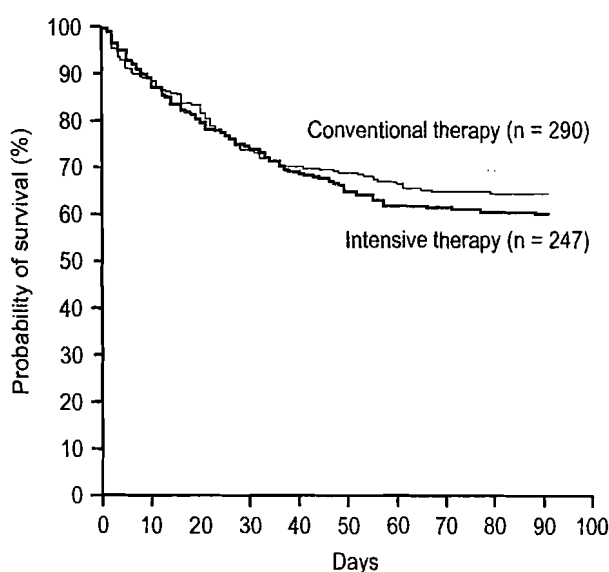
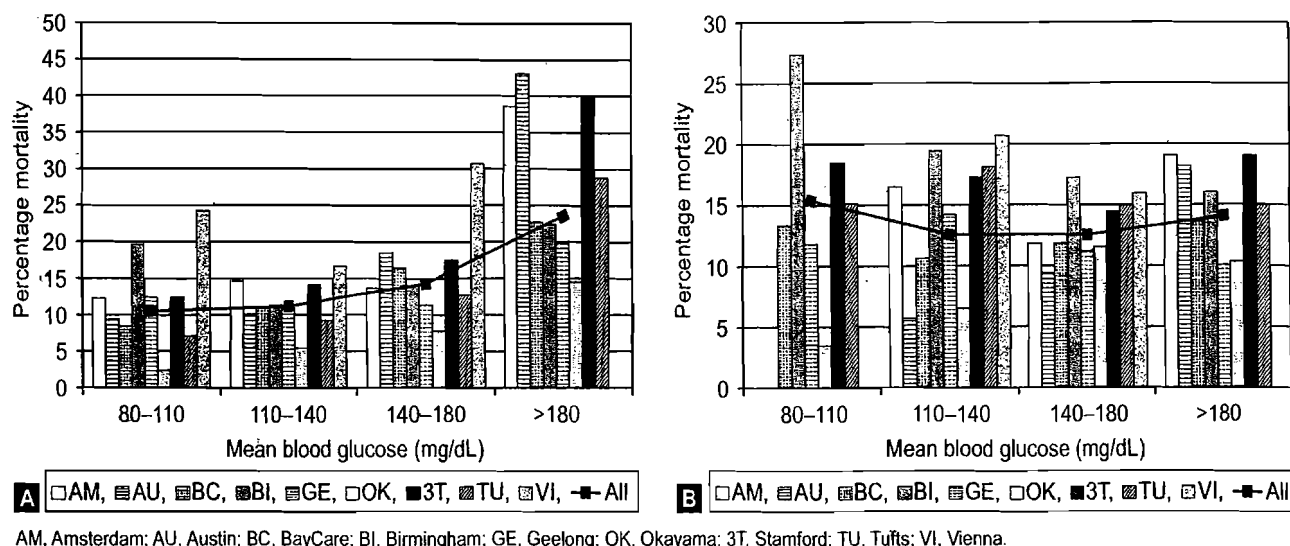


FIG. 3: Kaplan-Meier curve for overall survival in Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study⁸



AM, Amsterdam; AU, Austin; BC, BayCare; BI, Birmingham; GE, Geelong; OK, Okayama; 3T, Stamford; TU, Tufts; VI, Vienna.

FIG. 4: Relationship of mean blood sugar levels and mortality in patients without and with pre-existing diabetes mellitus. **A**, Nondiabetics and **B**, diabetics²⁵

at admission may be associated with poorer outcome.²⁶⁻³⁰ Single-center and multicentric RCTs^{31,32} in various subset of neurosurgical patients has shown the reduction of infections and length of stay in patients with intensive glycemic control (80–110 mg/dL) as compared to less intense control (180–200 mg/dL). However, this was associated with a statistically significant increase in the incidence of hypoglycemia. However, it is unclear whether intensive glycemic control in this subset of patients will improve mortality. Another important concern is the level of hypoglycemia tolerated by the brain. Studies indicate that the hypoglycemic threshold in acute brain insults corresponds to a blood glucose level of 80 mg/dL. However, optimal assessment of hypoglycemic threshold may vary from patient to patient and would require monitoring with a microdialysis catheter.³² Limited studies exist comparing moderate glycemic control with intensive glycemic control in patients with neurological insult.

OTHER PARAMETERS OF GLYCEMIC METRICS IN INTENSIVE CARE UNIT

Apart from hyperglycemia, which is perhaps the most widely studied, there are other aspects of glycemia which are clinically relevant in the ICU. These are hypoglycemia and glucose variability.

Hypoglycemia (Table 1)

Since the era of tight glycemic control began in the past decade, hypoglycemia in the ICU has emerged as an important metabolic complication. Incidence of severe hypoglycemia (defined as at least one blood glucose level <40 mg/dL) varies largely in published literature. The following table depicts the incidence of severe hypoglycemia in different studies.

TABLE 1 Hypoglycemia in insulin trials in intensive care unit

Study	Hypoglycemia (blood sugar <40 mg/dL)	
	Intensive (%)	Conventional (%)
Van den Berghe et al. 2001 ⁶	5	0.7
Van den Berghe et al. ⁷	18.7	3.1
WISEP ⁸	17	4.1
NICE-SUGAR ⁹	6.8	0.5
Glucontrol ¹⁰	7	2.7

WISEP, Volume Substitution and Insulin Therapy in Severe Sepsis; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation

The clinical significance of the iatrogenic episodes of hypoglycemia is unclear, especially when these episodes are identified and treated early. Some authors believe that even the iatrogenic hypoglycemia is a marker of poor outcome and directly related to the severity of illness with no direct bearing on mortality or morbidity. Kosiborod et al.³³ in a large retrospective analysis of over 17,000 patients with acute myocardial infarction found that spontaneous hypoglycemia was associated with a higher mortality in comparison to patients with no hypoglycemia. In contrast, patients developing hypoglycemia secondary to insulin therapy showed no change in mortality in comparison to patients with no hypoglycemia. This could suggest that spontaneous hypoglycemia is more likely a marker of severe illness and hence could predict a poor outcome.³³

Similarly, other studies have showed no association between hypoglycemia and mortality.³⁴

Meanwhile, in a retrospective case-control study of a mixed medical-surgical ICU, hypoglycemia was associated

with an increased risk of death after multivariate analysis (odds ratio: 2.28; confidence interval 1.41–3.7), but on balance benefits of glycemetic control far outweigh the risks.³⁵ This study also identified some of the common risk factors for hypoglycemia, which included, bicarbonate-based fluid during continuous venovenous hemofiltration, decreased rate or interruption of nutritional support, need for inotropic support, sepsis, female sex, prior diabetes, and octreotide use. Despite the lack of clear data regarding the dangers of hypoglycemia in the ICU, it makes physiological rationale to believe that prolonged hypoglycemia and recurrent hypoglycemia are associated with increased risk of neuronal injury. Identifying the clinical symptoms and signs of hypoglycemia in a critically ill patient is extremely difficult in view of the use of sedation, inability to mount the characteristic sympathetic response and debilitated state. Furthermore, the long-term neurocognitive consequences of prolonged hypoglycemia are poorly understood.

Role of Glucose Variability

Egi et al.³⁶ demonstrated that in a heterogeneous group of critically ill patients, glucose variability (defined as the standard deviation of glucose) was an independent predictor of mortality and more powerful than the mean glucose concentration achieved. In another study,³⁷ observation of 46,474 blood glucose and insulin data in a surgical ICU showed a statistically significant change between two blood glucose values among nonsurvivors compared to survivors. This is despite the mean glucose between the two groups being nearly equal, thus indicating that glucose variability in the critically ill surgical patients seems to be an independent predictor of outcome. Krinsley's³⁸ retrospective analysis of critically ill patients in a single ICU revealed that for a given blood sugar range increased variability increased the risk of mortality.³⁸

There was almost a threefold increase in mortality in the same mean glucose range when the glycemetic variability increased from lowest quartile to the highest quartile. In a large retrospective analysis of prospectively collected data from the Australian and New Zealand Intensive Care Society data base over 66,000 patients early (within 24 hours of ICU admission) hypoglycemia and early (within 24 hours of ICU admission) glucose variability independently increased the risk of mortality with the latter having a larger effect than hypoglycemia on mortality.³⁹ Hypoglycemia increases the tendency for glycemetic variability. Clinically, it is a normal tendency to treat glycemetic with a glucose bolus, which increases the risk of glycemetic variability. It thus seems that in the tight glycemetic control patients, this increased glycemetic variability negates the effect of tight glycemetic control. *In vitro* studies show that fluctuating glucose levels induce apoptosis more robustly than sustained hyperglycemia, causing endothelial activation and increased oxidative stress.⁴⁰ Similarly, *in vivo* rapid fluctuations in glycemetic control are associated with increased oxidative stress and

this relationship seems to be more important than the level of chronic sustained hyperglycemia among type II diabetics.⁴¹ Future studies are needed to examine and report the effect of glucose variability. This may be an important metric to follow. Investigators have used many such measures in literature, but a standardized "language" and metric to describe "variability" has to be established. Additionally, prospective evaluation regarding glycemetic variability is needed to determine whether this is an epiphenomena associated with severity of illness or in itself a physiological abnormality requiring a targeted intervention.

Glucose Monitoring

The gold standard for glucose monitoring in the inpatient setting is the central laboratory measurement of plasma glucose. Plasma blood glucose is preferred over whole blood glucose to eliminate the influence of factors like hematocrit on the measurement. The values of measurement will also depend on the sample source with arterial sample typically having a value 10 mg/dL higher than venous blood, which in turn is 5 mg/dL higher than the capillary blood. These differences may be further accentuated in the presence of hyperglycemia.

Due to the practical convenience and ease of measurement, capillary point-of-care finger-prick meters have become a routine method of glucose monitoring at home, in the hospital wards, as well as in the ICU. These meters are based on glucose oxidase or glucose dehydrogenase methods. This measurement using glucose oxidase method is likely to be influenced by catecholamines, bilirubin, uric acid and the presence of certain drugs like paracetamol. Glucose meters using the glucose dehydrogenase reaction are less likely to be influenced by the above factors, but may detect sugars other than glucose (such as mannose, xylose and icodextrin), thus causing possible overestimation of the blood glucose concentration.^{42,43}

Measuring capillary blood glucose in the critically ill patients is fraught with numerous practical problems, which could distort the results. These factors include hypotension, hypoperfusion, acidosis, anemia, and hypothermia. Further, it tends to be labor intensive for the nursing, especially when frequent measurements are needed. Accordingly, multiple continuous glucose monitoring systems are being evaluated for inpatient use. This method has been used successfully in outpatient management of diabetes, wherein subcutaneous sensors are placed and interstitial glucose measured using the same principle as in point-of-care method. In view of the similarity in the method, the same practical problems seen in the point-of-care method are found in these devices.⁴⁴⁻⁴⁷

Glycemic Control and Nutrition

Nutrition is an important aspect of glycemetic control in the ICU. It is well-known that inadequate nutrition is associated with poor outcomes. However on the contrary, overfeeding

is harmful as well and associated with increased risk of infections, hyperglycemia, etc. It is now proposed that if about 60% of caloric needs are met, this suffices to achieve a nitrogen balance equal to "full" dose of feeds. Thus appropriate dosing and timing of administration of feeds is important part of glycemic control in the ICU.^{48,49}

CONCLUSION

Hyperglycemia is common metabolic problem encountered in the ICU. Today, we have a better understanding about critical cellular pathways that can become deranged with prolonged and uncontrolled hyperglycemia. Recent research has also paved the way for better understanding of the complex relationship between nutritional status, protein catabolism and insulin-resistant states. For most patients, moderate glycemic control is appropriate and new technologies such as continuous glucose sensors may help alleviate the risks associated with excessive glucose variability as well as severe hypoglycemia.

REFERENCES

- Cely CM, Arora P, Quartin AA, et al. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest*. 2004;126(3):879-87.
- Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med*. 2014;40(7):973-80.
- Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery*. 2000;46(2):335-42.
- Laird AM, Miller PR, Kilgo PD, Meredith JW, et al. Relationship of early hyperglycemia to mortality in trauma patients. *J Trauma*. 2004;56(5):1058-62.
- Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78(12):1471-8.
- Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-67.
- Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449-61.
- Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-39.
- Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-97.
- Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009;35(10):1738-48.
- Hoang QN, PisaniMA, Inzucchi S, Hu B, et al. The prevalence of undiagnosed diabetes mellitus and the association of baseline glycemic control on mortality in the intensive care unit: a prospective observational study. *J Crit Care*. 2014;29(6):1052-6.
- Siegelaar SE, Hickmann M, Hoekstra JB, et al. The effect of diabetes on mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2011;15(5):R205.
- Lang CH, Dobrescu C, Bagby GJ. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology*. 1992;130(1):43-52.
- Khani S, Tayek JA. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. *Clin Sci (Lond)*. 2001;101(6):739-47.
- Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. *Intensive Care Med*. 2003;29(4):642-5.
- Nielson CP, Hindson DA. Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentrations in vitro. *Diabetes*. 1989;38(8):1031-5.
- Vanhorebeek I, Gunst J, Derde S, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *J Clin Endocrinol Metab*. 2011;96(4):E633-45.
- Devlin JT, Hirshman M, Horton ED, et al. Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes*. 1987;36(4):434-9.
- Patel BK, Pohlman AS, Hall JB, et al. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. *Chest*. 2014;146(3):583-9.
- Stoll B, Puiman PJ, Cui L, et al. Continuous parenteral and enteral nutrition induces metabolic dysfunction in neonatal pigs. *JPEN J Parenter Enteral Nutr*. 2012;36(5):538-50.
- Hooper MH, Marik PE. Controversies and misconceptions in intensive care unit nutrition. *Clin Chest Med*. 2015;36(3):409-18.
- MacGregor IL, Gueller R, Watts HD, et al. The effect of acute hyperglycemia on gastric emptying in man. *Gastroenterology*. 1976;70(2):190-6.
- Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*. 2006;55(11):3151-9.
- Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009;180(8):821-7.
- Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care*. 2013;17(2):R37.
- Kushner M, Nencini P, Reivich M, et al. Relation of hyperglycemia early in ischemic brain infarction to cerebral anatomy, metabolism, and clinical outcome. *Ann Neurol*. 1990;28(2):129-35.
- Kimura K, Iguchi Y, Inoue T, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci*. 2007;255(1-2):90-4.
- SaliMA, Hadjizacharia P, Dubose J, et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. *Am Surg*. 2009;75(1):25-9.
- Jeremitsky E, Omert LA, Dunham CM, et al. The impact of hyperglycemia on patients with severe brain injury. *J Trauma*. 2005;58(1):47-50.
- Bilotta F, Spinelli A, Giovannini F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. *J Neurosurg Anesthesiol*. 2007;19(3):156-60.
- Bilotta F, Caramia R, Paoloni FP, et al. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology*. 2009;110(3):611-9.
- Vespa P, Boonyaputthikul R, McArthur DL, et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Crit Care Med*. 2006;34(3):850-6.
- Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA*. 2009;301(15):1556-64.
- Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med*. 2006;34(11):2714-8.
- Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med*. 2007;35(10):2262-7.
- Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. 2006;105(2):244-52.
- Dossett LA, Cao H, Mowery NT, et al. Blood glucose variability is associated with mortality in the surgical intensive care unit. *Am Surg*. 2008;74(8):679-85.
- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36(11):3008-13.
- Bagshaw SM, Bellomo R, Egi M, et al. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care*. 2009;13(3):R91.

40. Risso A, Mercuri F, Quagliaro L, Damante G, et al. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab*. 2001;281(5):E924-30.
41. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295(14):1681-7.
42. Wahl HG. How accurately do we measure blood glucose levels in intensive care unit (ICU) patients? *Best Pract Res Clin Anaesthesiol*. 2009;23(4):387-400.
43. Draft Guidance for Industry and Food and Drug Administration Staff. (2014). Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use. [online] Available from: <https://www.federalregister.gov>. [Accessed October, 2016].
44. Klonoff DC, Buckingham B, Christiansen JS, et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011;96(10):2968-79.
45. Kopecký P, Mráz M, Bláha J, Lindner J, et al. The use of continuous glucose monitoring combined with computer-based eMPC algorithm for tight glucose control in cardiosurgical ICU. *Biomed Res Int*. 2013;2013:186439.
46. Boom DT, Sechterberger MK, Rijkenberg S, et al. Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial. *Crit Care*. 2014;18(4):453.
47. Holzinger U, Warszawska J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. *Diabetes Care*. 2010;33(3):467-72.
48. Krenitsky J. Glucose control in the intensive care unit: a nutrition support perspective. *Nutr Clin Pract*. 2011;26(1):31-43.
49. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs. full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795-803.

Reversal of Bleeding on Anticoagulants: New Options

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INTRODUCTION

Anticoagulants are increasingly being prescribed in today's clinical practice either to prevent or to treat a variety of thrombotic complications. Major indications for anticoagulation are treatment of acute coronary syndrome, prevention and treatment of deep vein thrombosis and pulmonary embolism, and prevention of thromboembolic complications in atrial fibrillation (AF). Bleeding is the most serious adverse effect of anticoagulation, which may be serious and life-threatening or may cause long-term debility. Need for anticoagulant reversal occurs in case of life-threatening bleeding where bleeding cannot be controlled by simple withdrawal of the agent or local application of pressure, or if a patient needs to undergo an urgent invasive procedure, such as emergency surgery.¹

Risk of bleeding varies with the choice of agent and intensity of anticoagulation. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, comparing two doses of dabigatran against warfarin in patients with nonvalvular AF, the risk of major bleeding was lower in the group receiving 110 mg of dabigatran compared to both 150 mg dabigatran and warfarin group (2.71% per year vs. 3.11 and 3.36% per year, respectively).² Compared to controlled clinical trial, setting risk of bleeding is higher in the real life scenario. In controlled clinical trials of vitamin K antagonists (VKAs), the incidence of major bleeding reported was about 0.5% per year.³ Whereas in a prospective observational study from Italy conducted in outpatient setting, overall bleeding complications were as high as 7.6% per year and incidence of major bleeding was 1.1% per year.⁴ Bleeding risk also varies with a number of host factors like age, body weight, and renal or hepatic function.⁵ Another important variable determining the risk of major bleeding is the indication for anticoagulation. Higher bleeding events were noted when VKAs were prescribed for peripheral vascular or cerebrovascular disease than for other indications.⁴ The Randomized, Phase II Study to Evaluate the

Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients after Heart Valve Replacement (RE-ALIGN) trial, where dabigatran was tested against warfarin in preventing thrombotic complications in patients with mechanical heart valve, had to be stopped early because of the higher risk of both bleeding (4% in dabigatran group vs. 2% in warfarin group) and thrombotic complications in dabigatran treated patients.⁶ This result is in sharp contrast with the results of RE-LY trial.²

The indication for anticoagulation in a particular patient must be kept in mind before prescribing specific reversal agent. For example, reversal of VKAs in a patient with prosthetic mitral valve and atrial fibrillation may risk valve thrombosis and systemic thromboembolic complications. A balanced approach is required to assess the benefits and risks associated with reversal of anticoagulation and a clear plan to restart the anticoagulation as early as feasible.¹ In this review, different strategies for reversal of individual agents are discussed. Specific emphasis is given on the reversal of newer anticoagulants.

VITAMIN K ANTAGONISTS

Vitamin K antagonists include warfarin, acenocoumarol, and phenprocoumon with important differences in their half-lives (36–42 h for warfarin, 9 h for acenocoumarol, and 90 h for phenprocoumon). Use of reversal agent in nonbleeding patients on VKAs and prolonged international normalized ratio (INR) is controversial. Currently, there is no published data supporting the hypothesis that a rapid return of prolonged INR to the desired range is associated with a reduction in bleeding events.¹ Some experts suggest the routine use of low dose oral vitamin K in patients presenting with warfarin associated coagulopathy, but not in patients presenting with acenocoumarol associated coagulopathy.⁷ Prompt reversal of anticoagulation is warranted in cases of uncontrolled bleeding or bleeding in a noncompressible site. Available options for reversal of anticoagulation in VKA

treated patients are vitamin K (oral and intravenous), fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), and recombinant activated factor VII (rFVIIa) with variable efficacy, safety, and time to reversal.

Vitamin K

Vitamin K antagonists act by inhibiting vitamin K dependent γ -carboxylation of coagulation factors II, VII, IX, and X and the most appropriate intervention to counteract the effect of VKAs is the administration of vitamin K. However, delayed onset of action is a major limitation of vitamin K in an actively bleeding patient. After intravenous administration of vitamin K, INR starts to drop within 2 hours, but it may take 12–16 hours for its complete normalization. After oral administration of vitamin K, normalization of INR may be delayed further (up to 24 h).¹ There is a concern regarding the risk of anaphylactoid reaction following administration of parenteral vitamin K; however, the incidence of anaphylactoid reaction is reported to be only 3 per 10,000 doses.⁸ A slow infusion may reduce the risk of this complication.⁸

The advantage of vitamin K is its sustained effect. Single slow intravenous dose of 10 mg vitamin K (Kapilin) should be given to every VKA treated patient with uncontrolled bleeding, either alone or in conjunction with other reversal agents. Oral vitamin K may be considered in non-life-threatening situation, where a delayed effect is acceptable.⁷

Fresh Frozen Plasma

In principle, FFP can correct VKA associated coagulopathy by replacing vitamin K dependent clotting factors. The biggest advantage of FFP is its widespread availability. However, recent evidence has raised question about its efficacy in quick reversal of VKA associated coagulopathy. In a retrospective analysis of 405 patients with VKA associated major bleeding events, INR remained uncorrected (INR >1.3) 1 day after starting FFP administration. In subgroup of patients with intracranial hemorrhage, this failure to correct INR was significantly associated with 30-day mortality.⁹ Another disadvantage of FFP is unavoidable delay in its administration because of the requirement of blood grouping, thawing process, and a long duration of infusion. In a retrospective analysis of 69 patients, this delay in administration was associated with failure of reversal of INR at 24 hours. Significant association was observed between delay in first dose of FFP and reversal of INR within 24 hours; every 30 minutes of delay in the first dose of FFP was associated with a 20% decreased odds of INR reversal within 24 hours.¹⁰ In addition, transfusion of FFP is also associated with volume overload, transfusion reaction including transfusion associated acute lung injury and small but definite risk of transmission of infection.

Despite its disadvantages, in situations where PCC is not available, FFP is still widely utilized along with vitamin K

in life-threatening VKA associated bleeding. Fresh frozen plasma is also useful when use of PCC is contraindicated. Recommended dose for FFP is 20–30 mL per kg body weight.

Prothrombin Complex Concentrate

Another way of replacing vitamin K dependent clotting factors is infusion of PCC. A large number of PCCs are available commercially. All of them contain vitamin K dependent factors II, IX, and X, and are standardized according to their factor IX content. They also contain differing amounts of factor VII; products with low or high quantities of factor VII are classified as either 3-factor or 4-factor PCCs, respectively. Most of the available PCCs contain variable quantities of antithrombotic factors, such as protein C, protein S, protein Z, and heparin. Furthermore, activated PCCs (aPCCs) are available which contain activated factor VII in addition to nonactivated factors II, IX, and X. Advantages of PCCs over FFPs are ability to administer them rapidly, small infusion volume, and no need for thawing or blood type matching. As PCCs undergo at least one virus inactivation process, they are associated with a lower risk of infection transmission compared to FFP.

In a multicenter, prospective, randomized trial of 216 patients with VKA associated major bleeding and INR above 2, 4-factor PCC was found to be noninferior to plasma in achieving hemostasis in 24 hours. However, PCC was found to be superior to plasma in normalizing INR (<1.3) within 30 minutes (62.2 vs. 9.6%). Both treatment options were found to have similar safety profile (adverse events, serious adverse events, thromboembolic events, and deaths).¹¹ In a systematic review of 18 studies and 654 patients comprising mostly intracerebral hemorrhage, urgent surgery or invasive procedure, and gastrointestinal bleeding, the ability of 4-factor and 3-factor PCCs in normalization of INR was tested. International normalized ratio decreased to ≤ 1.5 within 1 hour after PCCs administration in 6 of 9 studies in the 3-factor group, and 12 of 13 studies in the 4-factor group. The authors concluded that more reliable correction of INR was seen in 4-factor PCC treated patients.¹² This data may have clinical implications. Currently, there is limited data available for activated form of PCC in treatment of VKA associated bleeding.

Risk of thromboembolic events must be kept in mind with PCC administration. In a meta-analysis of 27 studies (total 1,032 patients) using 3-factor and 4-factor PCCs for reversal of VKA associated coagulopathy, the incidence of thromboembolism was found to be 0.7% and 1.8%, respectively.¹³ Caution must be exercised while prescribing PCC in patients with acute arterial thrombosis, disseminated intravascular coagulation and other coagulopathic states.

Prothrombin complex concentrate at a dose of 25–50 IU/kg is recommended as the initial choice for rapid reversal of VKA associated bleeding. International normalized ratio must be checked in 15–60 minutes time and every 6–8 hours

thereafter. Fresh frozen plasma may be considered if INR remains elevated above 1.4, after 24–48 hours.⁸

Recombinant Activated Factor VII

Recombinant activated factor VII has the ability to reverse the INR rapidly, like PCC, but it has been associated with a relatively high thrombosis rate (12.8–24%) and is not recommended routinely for the management of VKA associated bleeding. However, in special circumstances where blood products cannot be used (e.g., Jehovah's witness), rFVIIa may be considered.⁸

In summary, VKAs should be discontinued in case of bleeding. If the bleeding cannot be stopped by local hemostasis measures or in cases of intracranial hemorrhage, urgent reversal must be attempted preferably with either 4-factor or 3-factor PCC if available or with FFP. Vitamin K must be administered intravenously in every bleeding patient. Vitamin K antagonists should not be reversed in case of intracranial hemorrhage associated with cerebral venous sinus thrombosis.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) has a relatively short half-life of 60–90 minutes and its anticoagulation effect wanes of in 3–4 hours after stopping continuous intravenous infusion.¹ Subcutaneously administered heparin has an unpredictable effect as an anticoagulant and frequently do not achieve target therapeutic level.¹⁴ Therefore, reversal of intermittent subcutaneous dose of heparin is recommended only if there is a prolongation of activated partial thromboplastin time (aPTT).⁸

Protamine

Protamine is a basic protein derived from fish sperm that binds with heparin and forms a stable complex. About 1 mg of protamine can bind 100 units of heparin. It has a short half-life of 7 minutes compared to 60–90 minutes half-life of UFH. Hence, the dosing of protamine should account for last 2–3 hours dose of heparin infused. For example, protamine dose for a patient on stable therapeutic heparin infusion of 1,000–1,250 units/h is 25–30 mg.^{1,8} Despite its proven efficacy in reversing the anticoagulant effect of heparin, the benefit of this reversal effect in real world patients has not been proven in clinical trials. In a randomized control trial, 120 patients received either protamine or saline to reverse the effect of heparin utilized during surgery.¹⁵ Heparin level, aPTT, and activated clotting time were all lower in the protamine treated group both at 20 minutes and 1 hour. However, there was no difference in blood loss, hematoma formation in the surgical site, or requirement of fluids and blood products in the two groups.

Anaphylaxis, hypotension, bradycardia, and bronchoconstriction are known dose dependent adverse effects of protamine. Patients with history of receiving protamine in the past or history of fish allergy or vasectomy and patients on neutral protamine Hagedorn insulin, are at a higher risk of these adverse reactions. Rate of administration of protamine should not exceed 20 mg/min and in any 10 minutes period, total dose of protamine should not be more than 50 mg.⁸ Higher dose of protamine can paradoxically increase bleeding, as protamine itself is a weak anticoagulant.⁸

In summary, protamine sulfate should be administered in patients treated with intravenous heparin infusion and having active bleeding not controlled by local hemostasis or in cases of intracranial hemorrhage. Dose of protamine is determined by the amount of heparin administered in last 2–3 hours. Protamine administration is indicated following subcutaneous heparin administration, only if the patient is actively bleeding and having a prolonged aPTT.

LOW MOLECULAR WEIGHT HEPARIN

Low molecular weight heparins (LMWHs) are produced by fractionation of heparin by chemical or enzymatic methods to lower molecular weight fraction (4,000–6,000 Da). They produce their anticoagulant effect by predominantly binding and neutralizing factor Xa with minimal effect on thrombin (factor IIa). Bleeding risk with LMWH varies with different formulations and dosing. In a Cochrane review of 19 randomized control trials, comparing LMWH and UFH for the treatment of venous thromboembolism, incidence of major hemorrhage were lower with LMWH (1.2 vs. 2%) overall. However, in a closure analysis, only tinzaparin had significantly lower risk of bleeding; whereas the bleeding risk was higher with enoxaparin (though statistically nonsignificant).¹⁶ Currently, there is no specific reversal agent for LMWH.⁸

Protamine

Protamine has variable neutralizing effect on different LMWH based on the molecular weight and sulfated charge density. For example, protamine has better reversal effect on highly sulfated tinzaparin compared to enoxaparin. Protamine mostly neutralizes the anti-IIa activity with little effect on anti-Xa. It can also improve the hemostasis by its ability to decrease tissue factor pathway inhibition by LMWH.⁸

Suggested dose for protamine is to give 1 mg per 100 anti-Xa units of LMWH given in the last 8 hours (where 1 mg of enoxaparin equals 100 anti-Xa units). A second dose of 0.5 mg per 100 anti-factor Xa units can be given if bleeding continues. If bleeding continues 8-hour after last dose of LMWH, a protamine dose of 0.5 mg per 100 anti-factor Xa units may be considered.^{1,8}

Other Reversal Agents

Some *in vitro* studies, animal studies, and small case series have suggested some role of rFVIIa in reversal of LMWH. However, because of its high thrombogenic potential, it should be considered only when protamine is either contraindicated or protamine failed to reverse bleeding.⁸ Activated PCC, PCC, or FFP have no role in reversing the bleeding effect of LMWH.⁸

To summarize, LMWH must be discontinued in case of active bleeding. Protamine may be considered in case the patient is on therapeutic anticoagulation and 3–5 half-lives of the particular compound has not elapsed. In patients on prophylactic dose of LMWH, reversal with protamine is not required. Consider rFVIIa in case protamine is contraindicated or bleeding is not controlled with protamine.

PENTASACCHARIDES

Pentasaccharides are newly developed class of synthetic anticoagulant that binds with antithrombin and predominantly inhibit the effects of factor Xa. Due to the lack of glycosaminoglycan saccharide residue, they do not bind with thrombin. Two commercially available molecules of this class, fondaparinux and idraparinux, differ by their half-lives with idraparinux having significantly longer half-life of 5.5 days compared to 15–20 hours for fondaparinux.¹ Currently, there is no reversal agent commercially available against these compounds. However, there is a biological plausibility in favor of using PCC, aPCC, and rFVIIa in bleeding patients on pentasaccharide anticoagulation. In a recent systematic review of 5 studies on PCC, aPCC, and rFVIIa for the reversal of pentasaccharide anticoagulation, authors concluded that the best available data support the use of rFVIIa for reversal of bleeding in pentasaccharide treated patients.¹⁷ However, individual studies included in the review were of poor quality. Potential risk of thrombogenicity is also high with rFVIIa.

More recently, a recombinant variant of antithrombin (AT-N135Q-Pro394) has been developed and preclinical studies has shown its efficacy to bind and neutralize fondaparinux.¹⁸

DIRECT ORAL FACTOR XA INHIBITORS

Three oral factor Xa inhibitors are currently approved for clinical use—rivaroxaban, apixaban, and edoxaban. The half-lives for these three agents are 5, 12, and 10–14 hours, respectively. For rivaroxaban and edoxaban, the major route of excretion is renal (66% and 50%, respectively); whereas apixaban is excreted mostly fecally (only 27% renal excretion).⁸ In the major clinical trials, the incidence of intracranial hemorrhage was significantly lower in patients treated with oral factor Xa inhibitors compared to warfarin, but the incidence of extracranial bleeding, particularly gastrointestinal bleeding, was higher with rivaroxaban and

edoxaban treated patients.¹⁹ Reversal agent for factor Xa inhibitors are still under investigation and currently, there is limited data available for the efficacy of conventional clotting factor concentrates in bleeding associated with these agents.

Activated Charcoal

Administration of activated charcoal, very early after ingestion of oral factor Xa inhibitors may be useful in reducing absorption of the drug. Effect of activated charcoal (50 g) on apixaban single dose (20 mg) was studied on 18 healthy human subjects.²⁰ When charcoal was administered at 2 and 6 hours postingestion, the area under concentration curve for apixaban, reduced to 50% and 28%, respectively, compared to same concentration curve without the administration of charcoal. Furthermore, the mean half-life of apixaban was reduced by approximately 5 hours (compared to 13.5 h without charcoal administration). Authors concluded that activated charcoal administration is useful in accidental overdose of apixaban up to 6 hours after exposure. However, because of the rapid absorption of rivaroxaban from stomach, activated charcoal may not be very useful in the elimination of rivaroxaban.⁸ Main drawback of charcoal administration is the requirement for a secured airway in an unconscious patient.

Hemodialysis

Hemodialysis is not expected to increase the elimination of oral factor Xa inhibitors and is not recommended for reversal of bleeding due to these compounds.⁸

Prothrombin Complex Concentrates

In the absence of clinically available reversal agent, PCC is recommended for controlling life-threatening bleeding in patients on oral factor Xa inhibitor.¹⁹ However, this recommendation is based on mostly laboratory or animal studies, few case reports or case series and one phase I trial on healthy volunteer.¹⁹ In a double blind, randomized, placebo controlled dose-ranging study, different doses of 4-factor PCC were tested in healthy volunteers following punch biopsy, for bleeding time and bleeding volume.²¹ All subjects were pretreated with single 60 mg dose of edoxaban. Intravenous administration of 4-factor PCC, dose-dependently reversed edoxaban's effects on bleeding duration and volume, with a complete reversal at 50 IU/kg.

Recombinant Activated Factor VII

Despite being a potent hemostatic agent, rFVIIa is not recommended, for reversal of bleeding in oral factor Xa inhibitor treated patients, because of its high prothrombotic potential.¹⁹

Fresh Frozen Plasma

There is scant information about the effect of FFP in reversal of oral factor Xa inhibitor and current guidelines are silent about its potential use in this scenario.^{8,19}

In summary, direct oral factor Xa inhibitors must be discontinued in a bleeding patient and local hemostatic measures must be applied. Consider administration of activated charcoal within 2 hours of their administration (except probably in rivaroxaban), provided the patients' airway is secured. In case the bleeding continues or in patients with intracranial hemorrhage, consider PCCs for reversing the effects of these drugs if the bleeding occurs within 3–5 half-lives of the last dose.

DIRECT THROMBIN INHIBITORS

Available direct thrombin inhibitors include parenteral compounds (indicated mostly in the setting of heparin induced thrombocytopenia) like bivalirudin, desirudin, argatroban, lepirudin, and oral agent dabigatran. Parenteral agents have very short half-life (25 min for bivalirudin to maximum up to 2 h for desirudin). A simple discontinuation of medication is sufficient to produce reversal of effect in cases any bleeding on these agents.⁸ In contrast, dabigatran has a prolonged half-life of 12–17 hours that may increase further in the presence of renal failure. Dabigatran etexilate, the prodrug (but not dabigatran itself), is a substrate for the multidrug efflux transporter P-glycoprotein and its absorption may be further enhanced when P-glycoprotein inhibitors (e.g., ketoconazole, verapamil, amiodarone, quinidine) are concomitantly administered, potentially enhancing the risk of toxicity. Idarucizumab, a specific reversal agent for dabigatran, has been approved recently by the United States Food and Drug Administration and European Medicine Agency.

Activated Charcoal

Activated charcoal can be administered orally to reduce the absorption of dabigatran within 2 hours of its ingestion. However, there is limited human data available to support its efficacy in a bleeding patient. Furthermore, caution must be exercised while prescribing activated charcoal to a patient with compromised airway.

Extracorporeal Removal

Certain pharmacological properties of dabigatran like its low protein binding (35%), a low-to-moderate steady state volume of distribution ($V_d = 0.7$ – 1.0 L/kg; based on a 70 kg patient), a low molecular weight (471.5 Da) makes extracorporeal therapy, a potentially attractive modality to enhance the elimination of dabigatran.²² This is especially true in the setting of renal failure as dabigatran is mostly

excreted unchanged through kidneys (>80%). At present, data supporting the usefulness of extracorporeal therapy is limited to anecdotal reports and case series. Furthermore, there are some practical limitations to its widespread use in emergency situations.²² Preparing the patient for extracorporeal therapy is time-consuming and placement of catheter in a coagulopathic patient may itself be hazardous. There is a higher risk of hypotension with extracorporeal therapy in a bleeding patient. A rebound effect of dabigatran was reported in some case series with an increase in the dabigatran concentration 4–8 hours after the discontinuation of intermittent hemodialysis. Despite these limitations, most experts recommend hemodialysis and continuous venovenous hemodiafiltration (CVVHDF) as effective strategies for emergency dabigatran removal.^{8,19} They suggest a high blood flow rates of 200–400 mL/min, and dialysate flow rates of 700 mL/min for at least 4 hours, followed by conventional continuous renal replacement therapy.⁸

Idarucizumab

Idarucizumab, if available, is the agent of choice for the emergency reversal of dabigatran and is discussed in detail in the next section.

Prothrombin Complex Concentrate

Prothrombin complex concentrates or aPCCs are not specific reversal agents against dabigatran. However, administration of PCCs and aPCCs have the ability to raise the levels of the vitamin K dependent coagulation factors, most notably prothrombin with consequent increase in thrombin generation. If the plasma concentration of thrombin is clearly increased in excess of the level of free dabigatran, theoretically, the antithrombotic effect of the drug can be minimized. Clinical effects of PCCs and aPCCs in the reversal of dabigatran associated bleeding have been reviewed in a recent article.²³ The authors reviewed preclinical studies, healthy volunteer studies, and case-reports. In 6 animal studies, the effect of PCCs and aPCCs on dabigatran induced coagulopathy was found to be dose dependent with sufficient doses of both PCC and aPCC (50 IU/kg) successfully reversing it.²³ No significant difference was observed between PCC and aPCC in the reduction of bleeding. The authors postulated that the lack of effectiveness of both PCCs and aPCCs at lower doses may be explained by insufficient increases in thrombin generation. The *ex vivo* effects of PCCs and aPCCs on dabigatran induced anticoagulation parameters were tested in two healthy volunteer studies with contradictory results, possibly explained by poor sensitivity of these parameters in monitoring the effects of dabigatran.²³ Case series and anecdotal reports included in the review consistently showed benefits of both PCCs and aPCCs in reversal of bleeding in dabigatran treated patients.²³ As expected in all these patients, PCC and aPCC were used as part of multimodal

treatment modalities. The authors concluded that due to widespread availability of PCCs and aPCCs compared to idarucizumab, their use may be warranted in emergency reversal of dabigatran, but a properly conducted randomized controlled trial is required to provide robust data regarding their efficacy, dose, and relative differences between various agents.²³

Recombinant Activated Factor VII

There is not enough evidence to support the use of rFVIIa in reversal of bleeding in dabigatran treated patients.⁸ In view of its high thrombogenic potential, rFVIIa should better be avoided in this setting.

Fresh Frozen Plasma

Fresh frozen plasma has been used as part of the multimodal strategies for emergency reversal of dabigatran. However, it is unlikely to be very useful in this setting, given the small quantity of coagulation factors present in FFP.

To summarize, in a patient with active bleeding, dabigatran must be discontinued. Activated charcoal may be administered within 2 hours of ingestion in patients with low risk of aspiration. In patients with renal insufficiency or in dabigatran overdose, consider hemodialysis or CVVHD to enhance its elimination, provided it is feasible and safe in an actively bleeding and coagulopathic patient. In the absence of idarucizumab, consider PCC for emergency reversal of dabigatran.

REVERSAL OF DIRECT ORAL ANTICOAGULANTS: NEWER OPTIONS

Newer oral anticoagulants targeting specifically thrombin or factor Xa have favorable pharmacokinetic properties with wide therapeutic window, short half-life, and predictable response without any requirement of therapeutic monitoring. Their efficacy in preventing thromboembolic events is now established. In a meta-analysis of 4 randomized controlled trials, compared to warfarin, direct oral anticoagulants (DOACs) significantly reduced stroke or systemic embolic events and all-cause mortality.²⁴ The meta-analysis has also shown a decreased risk of intracranial hemorrhage with DOACs.²⁴ Despite the attractive pharmacokinetic properties and proven efficacy, clinicians are still reluctant to use these agents in their clinical practice and one major concern is certainly lack of effective reversal agent.^{5,25,26} Fortunately, idarucizumab is now approved and a number of new reversal agents are under various stages of development.

Idarucizumab

Idarucizumab is a humanized mouse monoclonal antibody fragment binding specifically to dabigatran with an affinity approximately 350 times stronger than thrombin. In addition to dabigatran, idarucizumab also irreversibly binds with

the active glucuronide metabolite of dabigatran.²⁷ Both idarucizumab and idarucizumab-dabigatran complexes are finally excreted renally. It has no direct activity on coagulation and platelet activation and expected to have less prothrombotic potential.^{19,25,27}

A phase 3 clinical trial, Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD), is under way. The study planned to enroll 500 patients in two categories—group A, those with serious bleeding requiring reversal and group B, those requiring urgent intervention that cannot wait for at least 8 hours. All patients are given 5 g idarucizumab, as two intravenous boluses of 2.5 g, each administered over 5–10 minutes within 15 minutes of each other. Primary endpoint of the trial is the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, based on central laboratory measurement of dilute thrombin time (dTT) or ecarin clotting time (ECT). A key secondary endpoint is the restoration of hemostasis.²⁷ An interim analysis of the first 90 patients enrolled in the trial (51 patients in group A and 39 in group B) has been published recently.²⁸ Elevated dTT and ECT were reversed in 100% of patients with baseline elevation of these parameters within minutes of idarucizumab administration. Hemostasis was restored at a median of 11.4 hours in 35 patients from group A in whom time to cessation of bleeding could be assessed. In 36 patients from group B who underwent an intervention, hemostasis was judged to be normal in 33 patients with only mild-to-moderate abnormality in the other three. One patient, in whom anticoagulant was not reinitiated, had a thrombotic event within 72 hours of idarucizumab dosing.

Andexanet

Andexanet alfa is a catalytically inactive, truncated recombinant factor Xa with ability to bind and reverse the effect of direct factor Xa inhibitors as well as LMWHs. Because of its potential to bind and inhibit tissue factor pathway inhibitors (TFPI), andexanet may cause transient elevations of D-dimer and prothrombin fragments 1 and 2, as well as transient elevated levels of thrombin generation.^{25,27} The clinical significance of this phenomenon of TFPI inhibition is uncertain.

In a randomized placebo controlled trial, the ability of andexanet bolus (800 mg intravenous bolus, phase 1) and bolus plus infusion (800 mg intravenous bolus followed by infusion of 8 mg/min for 120 min, phase 2) to reverse the anticoagulation effect of apixaban [Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors (ANNEXA)-A] and rivaroxaban (ANNEXA-R) were tested on healthy older volunteers.²⁹ Primary outcome measure was change in anti-factor Xa activity. With andexanet bolus, anti-factor Xa activity was reduced by 94% in apixaban treated participants (compared to 21% in those who received placebo) and thrombin generation was fully restored in 100% within 2–5 minutes. Among the rivaroxaban treated participants,

anti-factor Xa activity was reduced by 92% among those who received an andexanet bolus (compared with 18% in those who received placebo) and thrombin generation was fully restored in 96%. These effects were sustained when andexanet was administered as bolus plus an infusion. Transient increases in D-dimer and prothrombin fragments 1 and 2 were observed, with no clinical thrombotic event. Currently, a phase 3 trial is underway (ANNEXA-4, NCT02329327), evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor associated acute major bleeding.¹⁹

Ciraparantag (PER977)

Ciraparantag is a synthetic, peptide-like molecule with ability to bind all DOACs via hydrogen bond and reverse their anticoagulant effect. It also binds with heparin, LMWH, and fondaparinux. In a phase 1, dose ranging study of ciraparantag in 80 healthy volunteers, pretreated with 60 mg edoxaban, baseline hemostasis as assessed by whole blood clotting time, was restored from the anticoagulated state within 10–30 minutes after administration of 100–300 mg of the drug and was sustained for 24 hours.³⁰ There was no evidence of procoagulant activity after ciraparantag dose. The full clinical therapeutic potential of this new agent can be ascertained only after phase 3 clinical trials.

CONCLUSION

Benefits of anticoagulant reversal must be balanced against the potential risk of promoting procoagulant state in a high risk patient. Agents should be avoided for reversing laboratory coagulation parameters in a nonbleeding patient, except probably in overdose situation. Anticoagulation effects must be reversed as quickly as possible in an actively bleeding patient or in patients who require urgent life-saving intervention. Numbers of proven interventions are available to reverse the anticoagulant effects of conventional anticoagulants. Nonavailability of effective reversal agents is still a major limitation for newer anticoagulants. Fortunately, a number of effective reversal agents against these newer anticoagulants are currently in various stages of development, with one (idarucizumab) already approved for clinical use.

REFERENCES

- Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost.* 2011;9:1705-2.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-51.
- Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:257S-98S.
- Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet.* 1996;348:423-8.
- Ghosh S. Unrestricted prescription of dabigatran: is it safe in a resource-limited setting. *Indian J Crit Care Med.* 2013;17:325-6.
- Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369:1206-14.
- Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost.* 2006;4:1853-63.
- Frontera JA, Lewin III JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care.* 2016;24:6-46.
- Menzin J, White LA, Friedman M, et al. Factors associated with failure to correct the international normalized ratio following fresh frozen plasma administration among patients treated for warfarin-related major bleeding. An analysis of electronic health records. *Thromb Haemost.* 2012;107:662-72.
- Goldstein JN, Thomas SH, Frontiero V, et al. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. *Stroke.* 2006;37:151-5.
- Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIb study. *Circulation.* 2013;128:1234-43.
- Voils SA, Baird B. Systematic review: 3-factor versus 4-factor prothrombin complex concentrate for warfarin reversal: does it matter? *Thromb Res.* 2012;130:833-40.
- Dentali F, Marches C, Pierfranceschi MG, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. *Thromb Haemost.* 2011;106:429-38.
- Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med.* 1986;315:1109-14.
- Dorman BH, Elliott BM, Spinale FG, et al. Protamine use during peripheral vascular surgery: a prospective randomized trial. *J Vasc Surg.* 1995;22:248-55.
- van Dongen CJ, van den Belt AGM, Prins MH, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev.* 2004;(4):CD001100.
- Elmer J, Wittels KA. Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. *Transfus Med.* 2012;22(2):108-15.
- Bianchini EP, Fazavana J, Picard V, et al. Development of a recombinant antithrombin variant as a potent antidote to fondaparinux and other heparin derivatives. *Blood.* 2011;117:2054-60.
- Niessner A, Tamargo J, Morais J, et al. Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management—a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. *Eur Heart J.* 2015;pii:ehv676.
- Wang X, Mondal S, Wang J, et al. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. *Am J Cardiovasc Drugs.* 2014;14:147-54.
- Zahir H, Brown KS, Vandell A, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation.* 2014;131:82-90.
- Awad NI, Brunetti L, Juurlink DN. Enhanced elimination of dabigatran through extracorporeal methods. *J Med Toxicol.* 2015;11:85-95.
- Grottko O, Aisenberg J, Bernstein R, et al. Efficacy of prothrombin complex concentrates for the emergency reversal of dabigatran-induced anticoagulation. *Crit Care.* 2016;20:115.
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet.* 2014;383:955-62.
- Ansell JE. Reversing the effect of oral anticoagulant drugs: established and newer options. *Am J Cardiovasc Drugs.* 2016;16:163-70.
- Connors JM. Antidote for Factor Xa Anticoagulants. *N Engl J Med.* 2015;373:2471-2.
- Lewy JH, Ageno W, Chen NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants guidance from the SSC of the ISTH. *J Thromb Haemost.* 2016;14:623-7.
- Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;373:511-20.
- Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med.* 2015;373:2413-24.
- Ansell JE, Bakhrin SH, Lauicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med.* 2014;371:2141-2.

Coagulopathy in Trauma

Chandrashish Chakravarty

INTRODUCTION

Hemorrhage after trauma happens from either bleeding from anatomical site of injury or due to coagulopathy and this differentiation needs to be made for a rational approach toward bleeding trauma patient (Table 1). In this chapter, coagulopathic bleed will be discussed.

INITIAL ASSESSMENT (TABLE 2)

Once a bleeding patient comes to the trauma bay, he/she needs quick clinical assessment to find out the source of bleeding. Stopping blood loss remains the first priority to prevent further dilutional coagulopathy from resuscitation fluids and blood products.

This may include trauma series X-rays of chest to look for hemothorax, X-ray of pelvis to look for displaced unstable fractures usually associated with massive blood loss and X-ray of extremities as required. Focused assessment by sonography in trauma (FAST) scan has gained tremendous importance in identifying intra-abdominal free fluid, which in a trauma victim should be assumed as blood. Now, extended FAST (EFAST) also helps to quickly rule out fluid (hemothorax) in pleural cavity.

If the patient is in shock and FAST is positive, he should be shifted to operating room (OR) for laparotomy and not to a computed tomography (CT) scanner.¹ Shock in a trauma victim is assumed to be hemorrhagic unless proven

TABLE 1 Differentiating traumatic bleed from coagulopathic bleed

Anatomical bleed	Coagulopathic bleed
<ul style="list-style-type: none"> • Result of direct trauma • Clinical diagnosis, trauma series X-rays or CT scans, FAST scan • Surgical control, embolization, tourniquet • Bleed from site of trauma/organ of injury • Cannot be prevented but needs to be stopped early • If uncontrolled can be compounded by coagulopathic bleed 	<ul style="list-style-type: none"> • Acute coagulopathy of trauma-shock, dilutional, drugs • APTT/PT/TT/platelet/fibrinogen, thromboelastography to diagnose • Blood products, hypothermia correction, acidosis correction • Diffuse oozing • Can be prevented in majority of patients • Worsens bleeding from anatomical site

CT, computed tomography; FAST, focused assessment by sonography in trauma; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

TABLE 2 Initial assessment of a bleeding trauma patient

Bleeding patient in trauma bay	Hemodynamically unstable	Hemodynamically stable
<ul style="list-style-type: none"> • Assessment • Chest X-ray • FAST • ABG with lactate • Small volume resuscitation with crystalloids • Tranexamic acid within 3 h • Predict requirement for MBT • Avoid hypothermia and correct acidosis 	<ul style="list-style-type: none"> • Get OR ready • Avoid plasma poor PRBC transfusion • Permissive hypotension to keep SBP >80 mmHg [or MBP >80 mmHg in severe TBI] • Early fibrinogen • Check ionized calcium • Noradrenaline may be used • Damage control surgery 	<ul style="list-style-type: none"> • Computed tomography scans • Monitor coagulation parameters • Act according to injuries noted • Take better history and start secondary survey

FAST, focused assessment by sonography in trauma; ABG, arterial blood gas; MBT, mycobacterium tuberculosis; OR, operating room; PRBC, packed red blood cell; SBP, systolic blood pressure; MBP, mean blood pressure; TBI, traumatic brain injury.

otherwise. Before starting the OR, the patient should be resuscitated with small volume of crystalloid boluses till blood products arrive to maintain a systolic blood pressure of around 80 mmHg except in severe traumatic brain injury patients where a mean blood pressure of 80 mmHg is desirable.¹ This permissive hypotension reduces blood loss from decreased pressure head, less dilutional coagulopathy, and less hypothermia from cold fluids.

If the patient is very acidotic or hypothermic, damage control surgery² should be performed for achieving quick hemostasis. The tripartite role of damage control laparotomy is to quickly look inside abdomen to stop bleeding from site of injury, preserve perfusion, and decontaminate. The time to achieve this is vital and more the time is lost, there is more coagulopathic bleeding leading to a vicious cycle. If no source of bleeding can be identified, pelvic angiogram and embolization³ of the bleeding vessel should be the next step.

THROMBOELASTOGRAPHY

Thromboelastography/rotational thromboelastometry (TEG/ROTEM) is a test to measure at the bedside efficiency of coagulation. It measures the speed and strength of clot formation. The speed at which the sample coagulates depends on the activity of the plasma coagulation system, platelet function, and fibrinolysis. The pattern of changes in strength and elasticity in the clot provide information about how well the blood can clot. This test displays four values: (i) the R value represents the time until the first evidence of a clot is detected, (ii) The K value is the time from the end of R until the clot reaches 20 mm and this represents the speed of clot formation, (iii) the maximum amplitude (MA) is a reflection of clot strength. It has been suggested in the recent guidelines of massive hemorrhage⁴⁻⁶ to diagnose the deficiency in hemostatic pathway and direct blood product transfusion. The advantages of TEG are that it is available at the point of care and helps to tease out the components of hemostatic defect, e.g., mean clot firmness (in ROTEM) <6 mm prompts fibrinogen administration or fresh frozen plasma (FFP)/prothrombin complex concentrate (PCC) may be transfused in case of delayed initiation of clot (reaction time, R >11 minutes). Maximum clot amplitude (MA) in TEG <50 shows platelet deficiency (also hypofibrinogenemia) whereas a pattern like a rat-tail (>3% decrease in clot strength after 30 min, A30 or LY30) shows hyperfibrinolysis.

ACUTE COAGULOPATHY OF TRAUMA—SHOCK OR ENDOGENOUS ACUTE COAGULOPATHY

Recent studies have shown that up to 25% of patients coming to the trauma bay are coagulopathic before getting any fluids. This has been termed acute coagulopathy of trauma-shock (ACoTS) or endogenous acute coagulopathy (EAC)

and primarily happens from tissue trauma hypoperfusion injury,^{7,8} which over activates the protein C pathway causing hyperfibrinolysis. Protein C, once activated, plays a dual role in fibrinolysis by firstly inhibiting thrombin generation (in turn by inhibiting cofactors V and VIII) and, secondly by consuming plasminogen activator inhibitor-1 (PAI-1). By the first mechanism, it decreases the availability of thrombin responsible for fibrin generation. It is important to remember that thrombomodulin expressed by damaged endothelium further reduces thrombin level by forming complex with it. By second mechanism, reduced PAI-1 causes hyperfibrinolysis by increased activity of tissue plasminogen activator (tPA).

This is a major shift from previous notion of coagulopathy in trauma, which either originated from overconsumption of coagulation factors (disseminated intravascular coagulation) or dilution of coagulation factors⁹ by fluids/plasma poor red blood cell (RBC) transfusion. These problems can be compounded by hypothermia and acidosis, which further inhibit the coagulation pathway. Acute coagulopathy of trauma-shock is independently associated with increased mortality, organ dysfunction and transfusion requirement.¹⁰

TRANEXAMIC ACID

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 study¹¹ subjected >10,000 trauma victims with significant hemorrhage to antifibrinolytic tranexamic acid (TXA) and found a decrease in mortality, if given early before 3 hours. It was administered as a 1 g bolus over 10 minutes followed by 1 g infusions over 8 hours in all patients. There was no increase in thrombotic events like acute myocardial infarction or stroke seen after administering this drug. Hyperfibrinolysis, as explained earlier, is central to development of ACoTS and hence addition of TXA to any patient with significant bleeding is rational. Tranexamic acid has become the standard of care in trauma since the CRASH-2 trial. If TXA is not available, ε-aminocaproic acid may be used instead. It is ten times weaker and needs to be given as infusion because of short half-life. Dosage: loading dose of 150 mg/kg followed by an infusion of 15 mg/kg/h.

PREDICTION OF MASSIVE TRANSFUSION

In adults, Massive transfusion (MT) is defined as replacement of more than 1 blood volume in 24 hours or >50% of blood volume in 4 hours (adult blood volume is approximately 70 mL/kg). Thus it is a post hoc definition when the damage has already been done. Hence, it is important to predict, which trauma victims may require MT and prepare the blood bank accordingly or trigger the "MT protocol" of the hospital. The assessment of blood consumption (ABC)¹² and the Trauma Associated Severe Hemorrhage scores¹³ used for predicting MT are discussed in this chapter.

Assessment of blood consumption score was first proposed by Nunez et al. in 2009 and later validated in larger trial. It is most clinical and easy to use. It involves:

- Systolic blood pressure at emergency room (ER) <90 mmHg
- Heart rate at ER >120/min
- Penetrating injury
- Focussed Assessment by Sonography in Trauma (FAST) positive for free fluid.

If at least two of these are present, it predicts the need for MT.

Massive Transfusion Protocol

After identifying the trauma victims who may require a MT or any patient who has already received four units of packed RBC (PRBC),¹⁴ the hospital blood bank and intensive care unit team must be intimidated to trigger the "MT protocol/pathway".

The basic premises of this MT protocol are:

- Arranging adequate FFP and platelet along with PRBC (ratio of FFP:platelet:PRBC is 1:1:1 or close to it)
- To arrange for at least 10 units of PRBC
- Arrange 3-4 units of FFP within 0.5 hour (time taken to thaw).

Certain general¹ rules apply to all severely bleeding trauma patients. Ionized calcium levels should be monitored during MT and iv-calcium replacement used if required. Generally accepted hemoglobin targets are 7 g/dL. In traumatic brain injury, a target of >9 g/dL should be used. Colloids like starch for resuscitation should be avoided and hypothermia prevented at every level. Although there was initial enthusiasm, 7.5% hypertonic saline-dextran combination did not prove to be of benefit in trauma resuscitation. Recent data hint that large volume 0.9% normal saline may cause more acidosis and balanced crystalloids should be used in small volume aliquots as resuscitation fluid.

USE OF FRESH FROZEN PLASMA AND PROTHROMBIN COMPLEX CONCENTRATE

The United States Army Institute of Surgical Research, after Iraq war revealed the concept of early FFP and platelet administration in bleeding war victims. The war taught us that whole blood is best for resuscitation as it has maximum hematocrit, platelet, and coagulation factors. As whole blood is difficult to obtain in civilian trauma settings, it was decided that a 1:1:1 ratio¹⁵ of PRBC:FFP:platelets shall be ideal.

Since plasma transfusion is not free of hazards, different studies followed to find out the best possible ratio, which balances the risk between coagulopathy and transfusion complications. There is still controversy and heterogeneity amongst the studies though most feel that the target should

be a FFP:RBC ratio somewhere between 1:2 and 1:1. Davenport et al.¹⁴ studied the thromboelastometric stability of clot formation and noted that plasma:RBC ratio should be between 1:2 and 3:4. Most studies did not show any benefit, but rather harm, in higher plasma:RBC ratio above 1:1.

Vitamin K-dependent coagulation factors usually are responsible for continuation of bleeding once fibrinogen is replaced. Fresh frozen plasma or four-factor PCC are good sources of factors II, VII, IX, and X. Prothrombin complex concentrate is more predictable in action. The lowest possible dose of PCC, which should be administered, is 20 IU/kg bodyweight because of its thrombogenicity.¹ Prothrombin time/international normalized ratio (INR) is the best possible guide to PCC therapy, if TEG is not available although unlike for warfarin reversal, INR is not a reliable marker of bleeding risk in emergency and trauma situations.¹⁶ High dose of PCC (25-50 U/kg) may be used to reverse factor Xa inhibitors like rivaroxaban/apixaban.^{17,18} It is increasingly likely that trauma patients on newer oral anticoagulants will be coming more often due to widespread use of these agents. Hemodialysis or idarucizumab¹⁹ may be used to reverse the effect of dabigatran in bleeding patients.

USE OF FIBRINOGEN OR CRYOPRECIPITATE

Volume resuscitation after massive blood loss leads to drop in fibrinogen levels at the earliest before coagulation factors reach critically low levels. In a recent large retrospective study, multivariate analysis²⁰ revealed that in massively transfused patients, those with a critically low level of fibrinogen on admission had the highest mortality. A fibrinogen level <100 mg/dL is an independent risk factor of mortality. Current guidelines¹ recommend a trigger of 150-200 g/dL for replacement of fibrinogen either from FFP or cryoprecipitate or fibrinogen concentrate in bleeding trauma victims. In general, administration of 3 g fibrinogen concentrate²¹ or 15-20 units of cryoprecipitate (50 mg/kg of cryoprecipitate) will increase plasma fibrinogen levels by 100 g/dL in a normal adult male who is severely bleeding. Point of care tests like thromboelastography²² is greatly helpful to decide, if fibrinogen should be administered early or not. It is important to note that FFP is not a good source of fibrinogen but rich in factors II, VII, IX, and X, whereas cryoprecipitate is also a rich source of von Willebrands factor and factor XIII. However, the safest and precise form of fibrinogen replacement remains fibrinogen concentrate.

PLATELETS

There is still controversy about the empirical transfusion of platelets in severely bleeding patients except in battlefields or those on dual-antiplatelet therapy. Platelet count usually drops to critical levels much late in hemorrhage and large volume crystalloid resuscitation. Hence, guidelines¹ suggest

a trigger of <50,000/cc for platelet transfusion in most civilian trauma. It should be kept at >100,000/cc in case of brain injury. Since risk versus benefit of platelet transfusion is uncertain, most believe in transfusing platelets once the laboratory values are available.

Those on antiplatelet therapy may benefit from desmopressin and recombinant factor VIIa (rFVIIa). Desmopressin is also indicated in trauma victims with von Willebrand disease.²³ It improves platelet aggregation in hypothermia²⁴ and acidosis and hence helps in hemostasis. The standard dosage used is 0.3 µg/kg diluted in 50 mL saline and infused over 30 minutes.

RECOMBINANT FACTOR VIIA

Role of rFVIIa in trauma situations remain controversial with some role²⁵ in blunt trauma particularly liver injury. It may be considered for bleeding control once acidosis and hypothermia is corrected, platelet and fibrinogen replaced, and surgery done, if possible. Blood and blood product transfusion must be optimized before rFVIIa is considered. The minimum effective dose is 60–90 µg/kg body weight. It is not recommended currently in isolated head trauma and in conjunction with PCC.

CONCLUSION

Of all trauma victims, 45% deaths¹¹ are attributed to bleeding. Coagulopathy sets in early after trauma. This needs prompt identification by conventional laboratory tests or TEG/ROTEM. Early aggressive blood/blood product based resuscitation has become the standard of care instead of large volume crystalloids. Early administration of fibrinogen concentrate and TXA may prove useful in severely bleeding patients.

REFERENCES

- Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):R76.
- Shapiro MB, Jenkins DH, Schwab CW, et al. Damage control: collective review. *J Trauma*. 2000;49(5):969–78.
- Velmahos GC, Toutouzas KG, Vassiliou P, et al. A prospective study on the safety and efficacy of angiographic embolization for pelvic and visceral injuries. *J Trauma*. 2002;53(2):303–8.
- Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.
- Grassetto A, De Nardin M, Ganzler B, et al. ROTEM®-guided coagulation factor concentrate therapy in trauma: 2-year experience in Venice, Italy. *Crit Care*. 2012;16(3):428.
- Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270–382.
- Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. *Injury*. 2007;38(3):298–304.
- Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma*. 2008;65(4):748–54.
- Johansson PI, Sorensen AM, Perner A, et al. Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. *Crit Care*. 2011;15(6):R272.
- MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003;55(1):39–44.
- CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.
- Cotton BA, Au BK, Nunez TC, et al. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma*. 2009;66(1):41–48.
- Maegele M, Paffrath T, Bouillon B. Acute traumatic coagulopathy in severe injury: incidence, risk stratification and treatment options. *Dtsch Arztebl Int*. 2011;108(49):827–35.
- Davenport R, Curry N, Manson J, et al. Hemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. *J Trauma*. 2011;70(1):90–5.
- Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62(2):307–10.
- Haas T, Fries D, Tanaka KA, Asmis L, et al. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? *Br J Anaesth*. 2015;114(2):217–24.
- Eerenberg ES, Kamphuisen PW, Slijpen MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573–9.
- Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol*. 2012;87(Suppl 1):S141–5.
- Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med*. 2015;373(6):511–20.
- Inaba K, Karamanos E, Lustenberger T, et al. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg*. 2013;216(2):290–7.
- Solomon C, Pichlmaier U, Schoechl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth*. 2010;104(5):555–62.
- Rugeri L, Levrat A, David JS, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost*. 2007;5(2):289–95.
- Singleton T, Kruse-Jarres R, Leissinger C. Emergency department care for patients with hemophilia and von Willebrand disease. *J Emerg Med*. 2010;39(2):158–65.
- Ng KF, Cheung CW, Lee Y, et al. Low-dose desmopressin improves hypothermia-induced impairment of primary haemostasis in healthy volunteers. *Anaesthesia*. 2011;66(11):999–1005.
- Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *J Trauma*. 2004;57(4):709–18.

Current Blood Transfusion Threshold in Intensive Care Units

Neeta Bose

INTRODUCTION

Blood transfusion is common in the critically ill and trauma patients. Blood is an indispensable product in the current medical practice.¹ Red blood cell (RBC) transfusion is used for improving oxygen delivery to tissues, most often to treat hemorrhage and anemia.² Red blood cell transfusion is important in the management of anemic patients and is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply.^{3,4} Blood is to be replaced by blood, especially beyond the initial stages of hemorrhagic shock, because with continuing blood loss tissues reach a critical oxygen delivery. Blood transfusion has been perceived as a safe and effective for almost 100 years. Lately, transfusion practice is moving toward a more restrictive approach due to emerging trial data and subsequent revised clinical guidelines and increased focus on the concept of blood management.^{2,5}

Although blood transfusion can be lifesaving, yet this has to be used judiciously for two simple reasons. One, blood and blood components are expensive and supplies are limited. Secondly, blood transfusion is essentially organ transplantation; hence, there can be serious adverse effects. Avoiding unnecessary transfusion is good for patients and conserving blood supplies. Clinical assessment and treatment is more important than just treating laboratory values.⁶ Physiology of the critically ill patients vary depending upon the primary illness and its severity, age, comorbid conditions, acute hemorrhage, and chronic anemia and thus, tolerance to low hemoglobin (Hb) differs as well as the benefit from transfusion. Hence, the need for transfusion is to be individualized, even though guidelines give cutoff values, risk versus benefit has to be weighed carefully by the treating physician.

ANEMIA DEFINITION

The World Health Organization defines anemia in men and women as an Hb <13 g/dL and <12 g/dL, respectively,⁷ and severe anemia as <8 g/dL.^{8,9} Anemia is common amongst the critically ill, 60% patients being anemic on admission to intensive care units (ICU) and 20–30% have a first Hb concentration of <9 g/dL.^{10–14} After 7 days, 80% ICU patients have an Hb <9 g/dL. There is a strong association between anemia and inferior outcomes, especially with associated cardiovascular disease.^{15–19} Anemia is more prominent in patients with septic shock with a mean admitting Hb level of 10.5 g/dL and in more than half of patients it decreases to <9 g/dL during the first 3 days of shock.^{11,12,20,21}

Anemia Causes

Anemia in the critically ill patient is multifactorial, but basic two fundamental processes happen: a shortened circulatory lifespan and/or diminished production of RBCs. Only 10–15% of patients have chronic anemia before ICU admission. Reasons can be enumerated as follows:

- Hemodilution—administration of intravenous fluids
- Blood loss
- Blood sampling
- Impaired erythropoiesis secondary to inflammation—in prolonged illness²²
- Rheologic changes inducing RBC removal via the reticuloendothelial system^{23,24}
- Decreased RBC production due to decreased endogenous erythropoietin levels, hyporeactive bone marrow, and immune-associated functional iron deficiency—all associated with critical illness.^{23,25}

TRANSFUSION INCIDENCE AND THE CURRENT PRACTICE IN TRANSFUSION

Approximately, 85 million are transfused annually worldwide.²⁶ In 2014/15 National Health Service Blood and Transplant issued 1.7 million units of RBCs to hospitals in England and North Wales. An estimated 430,000 patients received a RBC transfusion in 2002.²⁷

Various studies indicate that there is widespread use of RBC transfusion in critically ill patients. Overall, 30–50% of ICU patients receive RBC transfusions.^{14,28} About 10% of all RBCs transfused nationally are given in general ICUs.¹³ Studies indicate that only 20% of transfusions are ordered to treat hemorrhage,¹¹ the majority are given for anemia.¹⁹

Following are the percentage of patients transfused in ICUs from all over the world:²

- Anemia and Blood Transfusion in Critically ill Patients (ABC) study (Western Europe)—37%¹¹
- Sepsis Occurrence in Acutely Ill Patients (SOAP) study (Europe)—33%²⁹
- The CRIT study (United States of America)—44.1%¹²
- Trauma patients from CRIT study (United states of America)—55.4%³⁰
- Transfusion Requirements in Critical Care (TRICC) Investigators (Canada)—25%³¹
- North Thames Blood Interest Group (United Kingdom)—53.4%³²
- American Burn Association (ABA) Multicenter Trials Group (United States, Canada)—74.4%³³
- Audit of Transfusion in Intensive Care in Scotland (ATICS) study (Scotland, United Kingdom) —39.5%.¹³

STUDIES ON TRANSFUSION

Intensive Care Unit Studies on Transfusion

Anemia and Blood Transfusion in Critically ill Patients study

Prospective multicenter observational study of 3,534 patients from 146 ICUs in Western Europe indicated that 37% patients were transfused in ICU. Mean pretransfusion Hb was 8.4 g/dL with around five units per patient transfused. Mean ICU length of stay was equal to 4.5 days and overall ICU mortality was 13.5%.¹¹

Sepsis Occurrence in Acutely Ill Patients Study

Prospective multicenter observational cohort study of 3,147 patients from 198 ICUs in Europe done in May 2002 revealed that 33% received transfusion.²⁹

The CRIT Study

356 It examined the relationship of anemia and RBC transfusion to clinical outcomes. This was a prospective study done in

various ICU's from 213 hospitals, over a period of 8 months in year 2000–2001 and total 4,892 patients were enrolled. Around 44% patients had received on an average four to five RBC transfusion and mean pretransfusion Hb was around 8.6 g/dL. The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality.¹²

Transfusion Requirements in Critical Care Study

The strongest evidence guiding transfusion policy in adult critically ill patients comes from the TRICC study. Patients from 25 ICU's in Canada between 1994 and 1997, with an expected stay of more than 24 hours with an Hb of ≤ 9 g/dL within 72 hours of admission and considered to be euvoletic, were registered. Randomization was done into two groups, a high Hb transfusion trigger of <10 g/dL the "liberal" group, or a lower trigger of <7 g/dL (the "restrictive" group). The restrictive group received 54% lesser units of blood and 33% received no blood transfusion versus all patients in the liberal group received transfusions. The 30-day mortality in the liberal group was comparable to general ICU population (23.3%), on the other hand, there was lower mortality in the restrictive group (18.7%), though not significant. Younger patients (age <55 years) and patients with low Acute Physiology and Chronic Health Evaluation II (APACHE II) score (<20); mortality at 30 days was significantly lower in the restrictive group. Also, there were lower new organ failures in the restrictive group whereas incidence of acute respiratory distress syndrome (ARDS) was higher in the liberal group. This study supports maintaining Hb between 7 g/dL and 9 g/dL.³¹

Perioperative Studies on Transfusion

Transfusion Requirements after Cardiac Surgery Trial³⁴

Transfusion Requirements After Cardiac Surgery (TRACS) study was a prospective, randomized, controlled conducted between February 2009 and February 2010 in an ICU at a university hospital cardiac surgery referral center in Brazil, wherein patients were randomly assigned to a liberal strategy of blood transfusion (to maintain a hematocrit of 30%, Hb 10.5 g/dL) or to a restrictive strategy (hematocrit of 24% and Hb 9.1 g/dL). The primary outcome was a composite endpoint, which included 30-day mortality and severe morbidity (known complications like cardiogenic shock, ARDS, or acute renal injury requiring dialysis or hemofiltration)^{31,35–37} occurring during the hospital stay and this was similar in the two groups. Secondary outcomes included all respiratory, cardiac, neurologic, and infectious complications; inflammatory complications; bleeding-requiring reoperation; and ICU and hospital lengths of stay were similar in both the groups. More patients in the liberal strategy group received a blood transfusion than in the

restrictive group (78% vs. 47%). Total number of transfused RBC units was significantly more in the liberal group (613 vs. 258). Independent of the treatment, patients who received an RBC transfusion had higher rates of complications after surgery, including 30-day mortality. The number of transfused RBC units was an independent risk factor for clinical complications or death at 30 days (1.2-fold higher risk of death at 30 days for each unit transfused). Transfusion of five or more RBC units was associated with higher mortality.³⁴

Association of Anaesthetists of Great Britain and Ireland

Allogeneic red cell transfusion is commonly used to improve the oxygen carrying capacity of blood during the perioperative period. Increasing arterial oxygen content by increasing Hb does not necessarily increase tissue oxygen delivery or uptake. Randomized studies in various surgical clinical settings nowadays consistently support the restrictive use of red cells with no evidence of advantage of maintaining patients at higher Hb thresholds (liberal strategy). Approximately, 2 million units of red cells were issued across the United Kingdom in 2011,³⁸ with surgical patients receiving approximately 40% of transfused allogeneic blood.^{39,40}

Transfusion Studies in Older Patient

Patients belonging to the elderly age group deserve separate mentions, who are admitted in the ICU or undergoing surgery, especially with increasing life expectancy and more number of operations being performed. Due to their limited reserves, their response to different clinical scenarios can vary and be unpredictable.

- In older patients (>65 years), preoperative hematocrit levels and postoperative outcomes in terms of mortality and cardiac events were found to be inversely correlative in a retrospective review of 310,311 patients. Even with mild anemia, there was 10% increase in events¹⁸
- Functional Outcomes in Cardiovascular patients Undergoing Surgical repair of hip fracture (FOCUS) trial:⁴¹ 2,016 patients ≥ 50 years of age (mean age 81.6 years), who had either a history of or risk factors for cardiovascular disease (in 62.9% cases), and whose Hb level was below 10 g/dL after hip fracture surgery were enrolled from 47 clinical sites in United States of America and Canada between July 2004 and February 2009. Patients were randomly divided into liberal transfusion strategy (an Hb threshold of 10 g/dL) versus a restrictive transfusion strategy (symptoms of anemia or at physician discretion for an Hb level of <8 g/dL). A liberal transfusion strategy, as compared with a restrictive strategy, did not reduce rates of death or inability to walk independently on 60-day follow-up (primary outcome) or reduce in-hospital morbidity in elderly patients at high-cardiovascular risk including cardiovascular event rates and other functional

measures (secondary outcome). Hence, there is no evidence that maintaining the Hb level above 10 g/dL was superior to transfusion for symptoms or maintaining an Hb level of <8 g/dL.⁴¹

- Red blood cell use and patient outcomes were observed in six ICUs in United Kingdom between August 2009 and December 2010. Anemic (Hb ≤ 9 g/dL) critically ill patients of age ≥ 55 years requiring ≥ 4 days of mechanical ventilation in ICU were either grouped into restrictive or liberal blood transfusion strategies. Fewer patients in the restrictive group were transfused postrandomization ($p < 0.001$) and received a median fewer RBC units. No major differences in organ dysfunction, duration of ventilation, infections, or cardiovascular complications were observed during intensive care and hospital follow-up. Mortality at 180 days postrandomization trended toward higher rates in the liberal group (55%) than in the restrictive group (37%).⁴²

Cochrane Database

Cochrane Database Published in 2012

It examined the evidence for the effect of transfusion thresholds on the use of red cell transfusion and for any effect on clinical outcomes. Nineteen trials involving 6,264 patients were included. Restrictive transfusion strategies reduced the risk of receiving a RBC transfusion by 39%. The volume of RBCs transfused was reduced on average by 1.19 units. Restrictive transfusion strategies did not affect the rate of adverse events compared to liberal transfusion strategies (i.e., mortality, cardiac events, myocardial infarction, stroke, pneumonia, and thromboembolism). Restrictive transfusion strategies were associated with a statistically significant reduction in hospital mortality but not 30-day mortality and also there was no reduction in functional recovery and hospital or intensive care length of stay.⁴³

Cochrane Database of Systematic Reviews 2016

This review summarized all randomized controlled trials (RCTs) that investigated whether it is safe to give blood transfusions when the blood count drops to between seven and eight (thereby reducing the number of transfusions), rather than giving transfusions at higher blood counts of 9 to 10. Total 31 relevant trials involving 12,587 participants were examined. Those receiving blood at lower Hb were 43% less likely to receive transfusion than those at higher Hb. There was no difference in 30-day mortality or morbidity, e.g., infection (pneumonia, wound infection, etc.), myocardial infarction, strokes and thus there was no difference in adverse events between the two groups. It was concluded that a policy of transfusing at lower Hb levels would reduce the amount of unnecessary transfusions to avoid the harmful side effects.⁴⁴

Transfusion in Bleeding Patients

TRIGGER Trial

Between September 2012 and March 2013, 936 patients across six hospitals in United Kingdom presenting with acute upper gastrointestinal bleeding, except for exsanguinating hemorrhage were enrolled. Patients were grouped in either a restrictive (transfusion when Hb concentration fell below 8 g/dL)—403 patients, or liberal (transfusion when Hb concentration fell below 10 g/dL)—533 patients, RBC transfusion policy. There was high recruitment rate for the liberal group and Hb concentration was similar. Fewer patients received RBC's in the restrictive group, though not significant. There was no significant difference in clinical outcomes.⁴⁵

RATIONALE FOR TRANSFUSION

Majority of oxygen, which is delivered to the tissues, is bound to Hb in the RBCs. Oxygen delivery [oxygen flux (DO_2)] is dependent on content as well as the cardiac output:

$$\text{DO}_2 (\text{oxygen flux}) = [\text{CO} \times \text{Hb} \times \text{saturation} \times \text{Huffners constant} (1.39)] + (0.023 \times \text{PO}_2)$$

In the resting state, there is four times oxygen delivery than the consumption, hence if Hb falls, e.g., during bleeding with a normal cardiovascular status, delivery of oxygen will remain adequate until hematocrit decreases below 10%. Increase in cardiac output, rightward shift of oxygen dissociation curve, and increased oxygen extraction can compensate for decreased oxygen content. Anemia decreases oxygen delivery by decreasing its content in blood. In healthy patients, DO_2 can be raised by increasing cardiac output by either raising the heart rate or the stroke volume. In critically ill patients, oxygen consumption and its extraction by tissues is very high and DO_2 may become more dependent on arterial oxygen content, thus making oxygen utilization pathologically dependent upon DO_2 . Therefore, anemia is not well tolerated in the critically ill. In contrast, in healthy individuals, lower Hb levels up to 5–6 g/dL may be tolerated before any clinical effects were noticed.

In a study of healthy resting individuals, who had undergone acute isovolemic reduction of their Hb to 5 g/dL (hematocrit of 15%),⁴⁶ some developed electrocardiogram (ECG) changes of myocardial ischemia, progressive increases in stroke volume and heart rate,⁴⁷ and therefore, the cardiac output, and a progressive decrease in the systemic vascular resistance, although there was hardly any evidence of decreased oxygen delivery. Of note, cognitive function measured by reaction time and immediate memory was impaired when the Hb concentration was reduced to 5–6 g/dL.⁴⁸ In healthy adult, compensatory mechanisms may be working fine to mount an optimal clinical response,

but this may be impaired in critically ill patients and in patients with underlying cardiovascular disease. Hence, in the past, keeping a target of 10 g/dL was being justified in the critically ill. Though, over the years, multicenter RCTs are indicating that target Hb levels of 7–8 g/dL are better in many patients.^{2,19,49–54}

In any clinical setting blood transfusion cannot be denied to create a control group for comparative study, but retrospective study in patients who deny blood transfusion, comparisons of clinical effect can be drawn between low versus high Hb. The deleterious effects of severe postoperative anemia can be understood in the following studies: in a retrospective study of 1,958 patients who underwent surgery and declined blood transfusion for religious reasons, the mortality was 1.3% in patients with preoperative Hb ≥ 12 g/dL and 33.3% in patients with preoperative Hb lesser than 6 g/dL. Risk of death increased with low preoperative Hb (< 6 g/dL) and this was more so along with associated cardiovascular disease. The results were similar during analyses of postoperative Hb and 30-day mortality or in-hospital morbidity.¹⁵ In a retrospective analysis, 300 postoperative patients who refused blood transfusion due to religious reasons were analyzed. The risk of death was low in patients with postoperative Hb levels of 7.1–8.0 g/dL, although morbidity occurred in 9.4%. As postoperative blood counts fall, the risk of mortality and/or morbidity rises and becomes extremely high below 5–6 g/dL.⁵⁵

Sepsis and septic shock is characterized by endothelial dysfunction leading to vascular leakage and vasodilatation. This results in relative and absolute hypovolemia leading to organ hypoperfusion (severe sepsis) and manifest cardiovascular compromise with diminished oxygen delivery and impaired tissue oxygenation (shock) not reversed by initial fluid therapy (septic shock).^{56,57} If shock persists, the result is progressive multiple organ failure (MOF) and mortality rates close to 50% and in some subgroup of patients up to 75%.⁵⁸ For hemodynamic stability, fast intravenous fluids, vasopressors, and thereafter RBC transfusion is administered to augment oxygen delivery. Patients with septic shock have relative and absolute hypovolemia and along with an abnormal microcirculation making their compensatory response to anemia less predictable without the help of RBC transfusion.^{59,60} Similarly, other groups of patients with less oxygen carrying capacity are patients with coronary artery disease, myocardial infarction, and acute brain injury. Red blood cell transfusion helps best before oxygen delivery falls down to critical level (DO_2 critical) to prevent tissue hypoxia and multiorgan failure. However, DO_2 and oxygen uptake (VO_2) relationship varies widely in critically ill patients with septic shock and VO_2 may not increase linearly in spite of increasing oxygen delivery following blood transfusion, caused by heterogeneous microcirculation (stagnant hypoxia).^{61,62} Due to storage, RBCs do not deliver oxygen as well due to biochemical and biomechanical alterations, which modify their shape and properties.⁶³ Another

reason for the lack of increase in oxygen consumption with DO_2 increase may be because of mitochondrial changes (cytopathic hypoxia) due to which the organ cells are unable to exploit the increase in available oxygen DO_2 .^{21,57,64} Most of the studies show that severe anemia is correlated with poor outcome, but data from randomized clinical trials also suggest that aggressive correction of anemia does not necessarily improve the outcome. Anemia may be only a marker for more severe primary disease.⁵⁸

DETERMINANT OF TRANSFUSION TRIGGERS

Transfusion of RBCs have a lifesaving role in bleeding patients, but most RBCs are transfused in nonbleeding patients with low Hb levels (anemia) because this is still the only means of achieving a momentary increase in Hb level.^{2,11,12} For many decades, transfusion was based upon the "10/30 rule" to maintain a blood Hb concentration above 10 g/dL (100 g/L) and a hematocrit >30%.⁴

However, due to issues of transmission of bloodborne pathogens and cost factor, transfusion practices were relooked into since 1980. The 1988 National Institutes of Health Consensus Conference on Perioperative RBC Transfusions suggested that no single criterion should be used as an indication for red cell component therapy, and that multiple factors related to the patient's clinical condition need to be considered.⁶⁵

Transfusion triggers are dependent on many factors:

- Evidence of bleeding and stability of patient
- Reason for admission (trauma and Grantmakers in Health)
- Patient wishes (Jehovah's witness)
- Comorbid conditions (such as ischemic heart disease).

BENEFITS AND RISKS OF TRANSFUSION

To get the maximum advantage of RBC transfusion and minimal risks, unnecessary transfusions need to be avoided so as not to expose patients to potential infectious or noninfectious risks. Risks due to transfusion can be dangerous; incidence can be as high as that due to motor vehicle accidents, firearm injuries, fall fatalities, and airplane fatalities, etc. The possible risks due to transfusion are human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), fever, life-threatening reaction, and fatal hemolysis.⁵³

Red Blood Cell Storage Lesion

Storage leads to biochemical and biomechanical alterations, which modify the RBCs leading to intracellular depletion of 2,3-diphosphoglycerate (2,3 DPG) and adenosine triphosphate and thereby reducing the oxygen-carrying

capacity of blood. Structural changes include loss of cellular membrane integrity leading to shape change and loss of deformability. This increases the fragility leading to increased red cell-endothelial interaction. There is decrease in the storage medium pH, increase in plasma potassium, release of free Hb and iron, and accumulation of bioreactive substances.⁶⁶ Together storage lesion mechanisms decrease the RBCs ability to deliver oxygen to the tissues and increase the immunomodulatory potential within the storage medium. Systematic reviews in the setting of surgery, critical illness, and bleeding have found no significant improvement in oxygen delivery or consumption, despite an increase in oxygen content.^{25,67,68} This is due to the hemodynamic response to increased blood viscosity and the loss of red cell function during preservation and storage.^{25,67-73}

Transfusion-related Risks: Infectious or Noninfectious

Risk of infection transmission, e.g., viral: HIV, HCV, etc. or bacterial are almost eliminated due to laboratory testing.^{60,74,75} Noninfectious complications can be immune-mediated: hemolytic, anaphylactic, and TRALI—incidence of TRALI varies from 1:534 to 1:17,000^{76,77} or nonimmune-mediated: procedural error (ABO incompatibility) and TACO—which is the leading cause of transfusion-related mortality (1:18–1:356).⁷⁸⁻⁸⁰ Red blood cells transfusion may be associated with transfusion-related modulation of the immune system, linked to storage lesion, which may worsen the existing systemic inflammatory response syndrome (SIRS) leading to multiorgan failure.^{66,81,82} Leukocyte reduction has shown to decrease the immunomodulating properties of stored RBCs, but the clinical benefit is still unknown, which is now routinely performed in most European countries.^{21,83-85}

Leukocyte Reduction

Two prospective multicenter observational study regarding anemia and the risks associated with transfusions, the ABC study (2002) and SOAP study (2008) executed by the same principal investigator from Brussels, using the same approach for analysis of their study, but found different results. The ABC study showed association between more transfusions and organ failure and mortality, whereas in the SOAP study, there was a higher survival rate in the transfusion group than in the other patients. This difference is likely to be due to differences in the blood transfusions per se. Heightened awareness of the risks of blood transfusion have led to safer blood preparation in terms of viral transmission. Leukodepletion has also been widely implemented. In the ABC study, 46% of centers indicated that they used leukodepleted blood most of the time, whereas in the SOAP study, 76% of centers were routinely using the same. Leukodepleted blood is now much more commonly used across Europe and this may account

for the differences in the 2002 and 2008 studies.²⁹ Hebert et al.⁸⁶ performed a study comparing patient outcomes before and after introduction of routine blood leukodepletion and noted reduced inhospital mortality rates. Other studies have also shown similar results with transfusion of leukodepleted blood.⁸⁷⁻⁸⁹ The risks related to transfusion are proportional to amount transfused and the duration of storage of transfused RBCs.^{68,90-92} In spite of measures ensuring safety during blood transfusion, there are certain risks. The Serious Hazards of Transfusion in 2014 (SHOT) estimated that direct risk of transfusion-associated death was around 4.5 per million blood components administered and major morbidity was 61.9 per million blood components administered. The most common cause of death was TACO.⁹³

Misuse of Blood and Blood products

Blood transfusion has been found to be as one of the five most overutilized therapeutic procedures in the United States.⁹⁴ There are instances, when blood and blood components are used indiscriminately without paying attention to guidelines and without a valid reason for deviation. An observational study from ICUs of Landspítali, Iceland during 6 months in 2010 showed that all adult patients who received blood, the mean Hb value before RBC transfusion was 8.7 g/dL, but in one-third of cases, it exceeded 10 g/dL.⁹⁵

There is also evidence from national audits⁹⁶ of transfusion practice that:

- Some patients are receiving the wrong blood components
- The choice of blood component is not always based on clinical findings and laboratory test values
- Patients are not always monitored for the adverse effects of transfusion and these effects are not always managed correctly
- Some patients are transfused unnecessarily.

Error prevention during transfusion and decision to transfuse is very vital to avoid any mishaps and over-transfusion. The impact of clinical decision support at computerized physician order entry and effect of education on RBC transfusions have been assessed to see for clinical patient outcomes.^{94,97} Electronic patient identification systems have been developed, which involve prompting staff to carry out key steps in the process and electronically identifying the patient via the scanning of the patient's identification bands and blood components to ensure the transfusion is given to the intended recipient. Examples of such systems are patient identification band, bar code, or radiofrequency identification.⁹³

GUIDELINES FOR TRANSFUSION PRACTICE

Following are a number of previous guidelines regarding the indications for RBC transfusion:

- American College of Physicians: Practice strategies for elective RBC transfusion⁹⁸

- Practice guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy:⁴⁹
 - Red blood cell transfusions not to be dictated by a single Hb "trigger"
 - No transfusion when the Hb >10 g/dL and definitely to be given when it is <6 g/dL
- Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report. American Society of Anesthesiologists 2006:⁹⁹
 - Red blood cells to be administered when Hb <6 g/dL in young and healthy patient, especially in acute situations
 - Red blood cells are unnecessary when Hb >10 g/dL
 - With anticipated blood loss—Hb value not important
 - Between 6 g/dL and 10 g/dL—RBC transfusion based on ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation
- National Institutes of Health Consensus Conference on perioperative RBC transfusion⁶⁵
- Perioperative blood transfusion for elective surgery—a national clinical guideline. Scottish Intercollegiate Guidelines Network; initially published in 2001, updated in 2004^{100,101}
- Guidelines for RBC and plasma transfusion for adults and children. Report of the Canadian Medical Association Expert Working Group, 1997.¹⁰² Recommendations are:
 - Physician prescribing transfusion of RBCs should be familiar with the indications, benefits, and risks
 - Documentation to be done in the patient's chart
 - RBCs-administered primarily to treat morbidity due to inadequate tissue oxygen delivery (resulting from a low RBC mass)
 - No single value of Hb, which requires transfusion—correlation with clinical condition needed
 - Red blood cell transfusion—not for intravascular volume expansion
 - Anemia should not be treated with RBC transfusions, if alternative therapies with fewer potential risks are available and appropriate
- Guidelines for Transfusion in the Trauma Patient—Standard Operating Procedure for Clinical Care 2006¹⁰³
- Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline, 2007¹⁰⁴
- The American Association of Blood Banks had laid down guidelines about Hb threshold and other clinical variables to initiate RBC transfusions in hemodynamically stable adults and children. Literature search was done from 1950 to February 2011 and number of patients receiving transfusion and the number of RBC units given were examined. The adverse effects like mortality, myocardial

infarction, cardiac events, pulmonary edema, stroke, thromboembolism, renal failure, infection, hemorrhage, mental confusion, functional recovery, and length of hospital stay were noted. Following recommendations were made:

- Recommendation 1: To adhere to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high quality evidence)
- Recommendation 2: To adhere to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or an Hb level of 8 g/dL or less (Grade: weak recommendation; moderate quality evidence)
- Recommendation 3: No recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (ACS) (Grade: uncertain recommendation; very low quality evidence)
- Recommendation 4: Transfusion decisions should be influenced by symptoms as well as Hb concentration (Grade: weak recommendation; low-quality evidence)⁵³
- The American College of Physicians has developed guidelines to treat anemia in adults with heart disease. Essentially, it is based on literature from 1947 to July 2012 with additions done in 2013. The various outcomes, which were evaluated for this guideline included mortality; hospitalization; exercise tolerance; quality of life; and cardiovascular events (defined as myocardial infarction, congestive heart failure exacerbation, arrhythmia, or cardiac death) and harms, including hypertension, venous thromboembolic events, and ischemic cerebrovascular events. One of the recommendations is using a restrictive RBC transfusion strategy (trigger Hb threshold of 7–8 g/dL compared with higher Hb levels) in hospitalized patients with coronary heart disease⁵⁴
- Transfusion practice and guidelines in Australian and New Zealand intensive care units: The study was undertaken to examine the relation between clinical practice and national guidelines for the transfusion in Australian and New Zealand ICUs. Data from 47 ICUs over a 5-week period in 2008 was taken, wherein 757 patients received RBCs. Bleeding was the main reason for administration of RBCs and the mean pretransfusion Hb was 7.76 g/dL with only few transfusions deviating from the guidelines. Transfusion practice of RBCs in Australian and New Zealand ICUs is restrictive and is concordant with guidelines¹⁰⁵
- Clinical Practice guidelines for RBC transfusion by:
 - The American College of Critical Care Medicine Task Force of the Society of Critical Care Medicine
 - The Eastern Association for the Surgery of Trauma Practice Management Workgroup
 - Recommendations regarding indications for RBC transfusion in the general critically ill patient:
 - Hemorrhagic shock
 - Acute hemorrhage and hemodynamic instability or inadequate oxygen delivery
 - Restrictive strategy of RBC transfusion (Hb ≤ 7 g/dL) is as effective as a liberal transfusion strategy (Hb ≤ 10 g/dL) in critically ill patients with hemodynamically stable anemia, except in patients with acute myocardial ischemia
 - Hemoglobin level not to be used as a “trigger” for transfusion; patient’s physiological parameters are also decisive. In the absence of acute hemorrhage, RBC transfusion should be given as single units
 - Consider transfusion if Hb ≤ 7 g/dL in critically ill patients requiring mechanical ventilation, resuscitated critically ill, stable cardiac disease
 - Red blood cell transfusion should not be considered as an absolute method to improve tissue oxygen consumption in critically ill patients
 - Red blood cell transfusion—beneficial in patients with ACS who are anemic (Hb ≤ 8 g/dL) on hospital admission
 - Recommendations regarding RBC transfusion in sepsis:
 - There is insufficient data for sepsis patients, individual assessment is required.
 - Recommendations regarding RBC transfusion in patients at risk for or with acute lung injury (ALI) and ARDS:
 - ALI and ARDS—common respiratory complication, hence avoid RBC transfusion after resuscitation is completed
 - Diagnose and report TRALI (transfusion-related ALI)—emerging as a leading cause of morbidity
 - Not to be used for weaning
 - Recommendations regarding RBC transfusion in patients with neurologic injury and diseases:
 - No benefit of liberal policy of transfusion in moderate-to-severe traumatic brain injury
 - Subarachnoid hemorrhage—assess individually in each patient
 - Recommendations regarding RBC transfusion risks:
 - Risk of SIRS and MOF
 - Leukodepletion—may reduce infectious complications
 - Recommendations regarding alternatives to RBC transfusion:
 - Recombinant human erythropoietin
 - Hemoglobin-based oxygen carriers
 - Recommendations regarding strategies to reduce RBC transfusion:
 - Low volume adult or pediatric blood sampling tubes

- Intraoperative and postoperative blood salvage
- Reduction in laboratory testing—reduction in phlebotomy volumes
- Transfusion guideline summary (The National Institute for Health and Care Excellence guidelines)—National Clinical Guideline Centre, 2015.⁹³

Red Blood Cells: Thresholds and Targets

- Use restrictive RBC transfusion thresholds for patients who need RBC transfusions and who do not:
 - Have major hemorrhage
 - Have ACS
 - Need regular blood transfusions for chronic anemia
- When using a restrictive RBC transfusion threshold, consider a threshold of 7 g/dL and an Hb concentration target of 7–9 g/dL after transfusion
- Consider a RBC transfusion threshold of 8 g/dL and an Hb concentration target of 8–10 g/dL after transfusion for patients with ACS
- Consider setting individual thresholds and Hb concentration targets for each patient who needs regular blood transfusions for chronic anemia
- Consider single-unit RBC transfusions for adults (or equivalent volumes calculated based on body weight for children or adults with low body weight) who do not have active bleeding
- After each single-unit RBC transfusion (or equivalent volumes calculated based on body weight for children or adults with low body weight), clinically reassess and check Hb levels, and give further transfusions, if needed.

Beyond the clinical assessment, guidelines give a template which can be followed and help the physicians not to overtransfuse. There has been an approximate 25% decline in the transfusion of RBCs in England in the last 15 years.¹⁰⁶ The RBC transfusion rate declined from 45.5 units to 36 units per 1,000 people between 1999 and 2009, and since then has dropped further to around 31.5 units per 1,000 people. The proportion of RBCs used between 1999 and 2009 in surgical patients has declined from 41 to 29% of all red cells transfused, and in medical patients has increased from 52% to 64% of all red cells transfused. Use in obstetrics and gynecology has remained stable at 6%.¹⁰⁷ A national audit of blood transfusion in 2014 showed that the proportion of red cell transfusions used in surgical patients continues to decline and was 27% of all red cells transfused with a corresponding increase in medical patients to 67%.¹⁰⁸

STRATEGIES TO MINIMIZE TRANSFUSION REQUIREMENTS

- Alternatives to blood transfusion for patients having surgery: cell salvage and tranexamic acid.⁹³

- Tranexamic acid to adults undergoing surgery and expected to have at least moderate blood loss (>500 mL)
- Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (>10% blood volume)
- Do not routinely use cell salvage without tranexamic acid
- Consider intraoperative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example, in cardiac and complex vascular surgery, major obstetric procedures and pelvic reconstruction, and scoliosis surgery)
- If bleeding, transfuse aggressively until bleeding controlled (avoid hypothermia, acidosis, and coagulopathy)
- If not bleeding, restrictive strategy in those who can tolerate it and more liberal in those that have evidence of ischemic end-organ dysfunction
- Use new, leukodepleted blood, if feasible.

CONTROVERSIAL ISSUES

Although it is clear that most of the studies support that restrictive RBC transfusion practices appear safe, but patients with ACSs, traumatic brain injury, and at risk for brain or spinal cord ischemia were not well represented. PubMed-cited studies (between 1974 and 2013) lack quality data regarding the same. Hence, the optimal Hb in such patients and in anemic patients with ongoing hemorrhage, with risk of significant bleeding, remains unknown. While clinical guidelines are important, two common adverse consequences of such recommendations are that they are often misapplied to patient populations outside of those intended, and secondly, there is misinterpretation of the policy itself. Physicians need to be encouraged to treat the patient and not the Hb level.¹⁰⁹

CONCLUSION

Anemia decreases the oxygen delivery to the tissues, hence the need of transfusion arises, but it is yet to be established whether doing so improves the clinical condition of the patient or not. There is ample of evidence that a restrictive policy of Hb 7–8 g/dL should be kept for transfusion. This Hb threshold will definitely decrease unnecessary transfusion, thus avoiding the harmful effects of blood transfusion. Clinical judgment is more important and not just treating values. Even in septic shock, Hb has to be maintained >7 g/dL. If patient is symptomatic, e.g., angina or is hemodynamically unstable then transfusion threshold should be at <10 g/dL. Patients of trauma or ongoing bleeding cannot be managed using Hb thresholds. Hospital's own transfusion guidelines may be helpful in transfusion practices and reducing unnecessary transfusions, but they cannot overshadow clinical judgment.

REFERENCES

- Amin M, Fergusson D, Wilson K, et al. The societal unit cost of allogeneic red blood cells and red blood cell transfusion in Canada. *Transfusion*. 2004;44:1479-86.
- Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med*. 2009;37:3124-57.
- Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. *Lancet*. 2007;370:415-26.
- Wang JK, Klein HG. Red blood cell transfusion in the treatment and management of anaemia: the search for the elusive transfusion trigger. *Vox Sanguinis*. 2010;98:2-11.
- Waters JH, Ness PM. Patient blood management: a growing challenge and opportunity. *Transfusion*. 2011;51(5):902-3.
- Norfolk N. Transfusion in critically ill, Chapter 7. *JPAC Handbook of Transfusion Medicine*. 5th ed. UK: TSO Publishing; 2013.
- Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107:1747-50.
- Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104:2263-8.
- World Health Organisation, Geneva. (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. [online] Available from: <http://www.who.int/vmnis/indicators/haemoglobin.pdf>. [Accessed November, 2016].
- Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med*. 2001;29:227-34.
- Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288(12):1499-507.
- Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med*. 2004;32(1):39-52.
- Walsh TS, Garrioch M, Maciver C, et al. Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines. *Transfusion*. 2004;44:1405-11.
- Walsh TS, Lee RJ, Maciver CR, et al. Anemia during and at discharge from intensive care: the impact of restrictive blood transfusion practice. *Intensive Care Med*. 2006;32:100-9.
- Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet*. 1996;348:1055-60.
- Hebert PC, Wells G, Tweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? Transfusion requirements in critical care (TRICC) Investigators and the Canadian Critical Care Trials Group. *Am J Respir Crit Care Med*. 1997;155:1618-23.
- Kulier A, Levin J, Rumpold-Seitlinger G, et al. Impact of preoperative anaemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation*. 2007;116:471-9.
- Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA*. 2007;297:2481-8.
- Retter A, Wyncoll D, Pearse R, et al. Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. *Br J Haematol*. 2013;160:445-64.
- Rosland RG, Hagen MU, Haase N, et al. Red blood cell transfusion in septic shock—clinical characteristics and outcome of unselected patients in a prospective, multicentre cohort. *Scand J Trauma Resusc Emerg Med*. 2014;22:14.
- Lars Broksø Holst. Benefits and harms of red blood cell transfusions in patients with septic shock in the Intensive Care Unit. *Dan Med J*. 2016;63:B5209.
- Walsh TS, Saleh EE. Anaemia during critical illness. *Br J Anaesth*. 2006;97:278-91.
- Hayden SJ, Albert TJ, Watkins TR, et al. Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med*. 2012;185(10):1049-57.
- McEvoy MT, Shander A. Anemia, bleeding, and blood transfusion in the intensive care unit: causes, risks, costs, and new strategies. *Am J Crit Care*. 2013;22:eS1-13.
- Napolitano LM. Scope of the problem: epidemiology of anemia and use of blood transfusions in critical care. *Crit Care*. 2004;8:S1-S8.
- Takei T, Amin NA, Schmid G, et al. Progress in global blood safety for HIV. *J Acquir Immune Defic Syndr*. 2009;52:S127-31.
- Wells AW, Llewelyn CA, Casbard A, et al. The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfus Med*. 2009;19:315-28.
- Walsh TS, McArdle F, McLellan SA, et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Crit Care Med*. 2004;32:364-71.
- Vincent JL, Sakr Y, Sprung C, Harboe S, et al. Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. Are blood transfusion associated with greater mortality rates? Results of the Sepsis Occurrence in acutely ill patients (SOAP Study). *Anesthesiology*. 2008;108:31-9.
- Shapiro MJ, Gettinger A, Corwin H, et al. Anemia and blood transfusion in trauma patients admitted to the intensive care unit. *J Trauma*. 2003;55:269-74.
- Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409-17.
- Rao MP, Boralessa H, Morgan C, et al. Blood component use in critically ill patients. *Anesthesia*. 2002;57:530-4.
- Palmieri TL, Caruso DM, Foster KN, et al. Effect of blood transfusion on outcome after major burn injury: A multicenter study. *Crit Care Med*. 2006;34:1602-7.
- Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after Cardiac Surgery—The TRACS Randomized Controlled Trial. *JAMA*. 2010;304:1559-67.
- DeFoe GR, Ross CS, Olmstead EM, et al. Northern New England Cardiovascular Disease Study Group. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. *Ann Thorac Surg*. 2001;71:769-76.
- Reeves BC, Murphy GJ. Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery. *Curr Opin Cardiol*. 2008;23:607-12.
- Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion*. 1999;39:1070-7.
- Bolton-Maggs PHB, Cohen H. (2012). The 2011 Annual SHOT Report. [online] Available from <http://www.shotuk.org/wp-content/uploads/summary-2011.pdf>. [Accessed November, 2016].
- Association of Anaesthetists of Great Britain and Ireland. Blood Transfusion and the Anaesthetist. Red Cell Transfusion 2. London: AAGBI; 2008.
- Shah A, Stanworth SJ, McKechnie S. Review Article: Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia*. 2015;70:10-9.
- Carson JL, Terrin ML, Noveck H, et al. Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. *New Eng J Med*. 2011;365:2453-62.
- Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. *Crit Care Med*. 2013;41:2354-63.
- Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2012;4:CD002042.
- Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review). *Cochrane Database Syst Rev*. 2016;10:CD002042.
- Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet*. 2015;386:137-44.
- Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA*. 1998;279:217-21.
- Weiskopf RB, Feiner J, Hopf H, et al. Heart rate increases linearly in response to acute isovolemic anemia. *Transfusion*. 2003;43:235-40.

48. Weiskopf RB, Kramer JH, Viele M, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology*. 2000;92:1646-52.
49. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology*. 1996;84:732-47.
50. Clinical Practice Guidelines. (2001). Appropriate Use of Red Blood Cells. [online] Available from: http://www.anzsb.org.au/publications/documents/UseRedBlood_001.pdf. [Accessed November, 2016].
51. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999-3054.
52. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91:944-82.
53. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med*. 2012;157-49.
54. Qaseem A, Humphrey LL, Fitterman N, et al. Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2013;159:770-9.
55. Carson JL, Noveck H, Berlin JA, et al. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion*. 2002;42:812-8.
56. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165-228.
57. Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. *Crit Care Med*. 2007;35:S441-8.
58. Perner A, Haase N, Wetterslev J, et al. Comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis (6S—Scandinavian Starch for Severe Sepsis/Septic Shock trial): study protocol, design and rationale for *Trials*. 2011;12:24.
59. Morisaki H, Sibbald WJ. Tissue oxygen delivery and the microcirculation. *Crit Care Clin*. 2004;20:213-23.
60. Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Crit Care Med*. 2006;34:S102-8.
61. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. *Crit Care Clin*. 2004;20:255-68.
62. Fernandes CJ, Akamine N, De Marco FV, et al. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care*. 2001;5:362-7.
63. Goldman D, Bateman RM, Ellis CG. Effect of decreased O₂ supply on skeletal muscle oxygenation and O₂ consumption during sepsis: role of heterogeneous capillary spacing and blood flow. *Am J Physiol Heart Circ Physiol*. 2006;290:H2277-85.
64. Sjövall F, Morota S, Hansson MJ, et al. Temporal increase of platelet mitochondrial respiration is negatively associated with clinical outcome in patients with sepsis. *Crit Care*. 2010;14:R214.
65. Consensus conference. Perioperative red blood cell transfusion. *JAMA*. 1988;260:2700-3.
66. Lelubre C, Piagnerelli M, Vincent JL. Association between duration of storage of transfused red blood cells and morbidity and mortality in adult patients: myth or reality? *Transfusion*. 2009;49:1384-94.
67. Hebert PC, McDonald BJ, Tinmouth A. Clinical consequences of anemia and red cell transfusion in the critically ill. *Crit Care Clin*. 2004;20:225-35.
68. Tinmouth A, Fergusson D, Yee IC, et al. Clinical consequences of red cell storage in the critically ill. *Transfusion*. 2006;46:2014-27.
69. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993;269:3024-9.
70. Berezina TL, Zaets SB, Morgan C, et al. Influence of storage on red blood cell rheological properties. *J Surg Res*. 2002;102:6-12.
71. McMahon TJ, Ahearn GS, Moya MP, et al. A nitric oxide processing defect of red blood cells created by hypoxia: deficiency of S-nitrosohemoglobin in pulmonary hypertension. *Proc Natl Acad Sci USA*. 2005;102:14801-6.
72. Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. *Proc Natl Acad Sci U S A*. 2007;104:17063-8.
73. Reynolds JD, Ahearn GS, Angelo M, et al. S-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. *Proc Natl Acad Sci USA*. 2007;104:17058-62.
74. Bolton-Maggs PHB, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. *Br J Haematol*. 2013;163:303-14.
75. Tinmouth AT, McIntyre LA, Fowler RA. Blood conservation strategies to reduce the need for red blood cell transfusion in critically ill patients. *Can Med Assoc J*. 2008;178:49-57.
76. Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. *Br J Haematol*. 2009;147:431-43.
77. Toy P, Gajic O, Bacchetti P, Looney MR, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood*. 2012;119:1757-67.
78. Bolton-Maggs PHB. Bullet points from SHOT: key messages and recommendations from the Annual SHOT Report 2013. *Transfusion*. 2014;24:197-203.
79. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion*. 2011;51:338-43.
80. Rana R, Fernández-Pérez ER, Khan SA, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. *Transfusion*. 2006;46:1478-83.
81. Vlaar APJ, Juffermans NP. Transfusion-related acute lung injury: a clinical review. *Lancet*. 2013;382:984-94.
82. Juffermans NP, Prins DJ, Vlaar APJ, et al. Transfusion-related risk of secondary bacterial infections in sepsis patients: a retrospective cohort study. *Shock*. 2011;35:355-9.
83. Lelubre C, Vincent J-L. Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: a systematic review. *Crit Care*. 2013;17:R66.
84. Fergusson D, Khanna MP, Tinmouth A, et al. Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. *Can J Anaesth*. 2004;51:417-24.
85. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion. *JAMA*. 2014;311:1317.
86. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA*. 2003;289:1941-9.
87. Fergusson D, Hebert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. *JAMA*. 2003;289:1950-6.
88. Tartert PI, Mohandas K, Azar P, et al. Randomized trial comparing packed red cell blood transfusion with and without leukocyte depletion for gastrointestinal surgery. *Am J Surg*. 1998;176:462-6.
89. Bilgin YM, van de Watering LM, Eijssman L, et al. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. *Circulation*. 2004;109:2755-60.
90. Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth*. 1997;44:1256-61.
91. Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. *Transfusion*. 1999;39:701-10.
92. Koch CG, Li L, Sessler DI, Figueroa P, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008;358:1229-39.
93. National Clinical Guideline Centre—NICE guideline—methods, evidence and recommendations, November 2015—Commissioned by the National Institute for Health and Care Excellence.

94. Goodnough LT, Maggio P, Hadhazy P, et al. Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion*. 2014;54:2753-9.
95. Oddason KE, Gu bjartsson T, et al. Inappropriate use of blood components in critical care? *Laeknabladid*. 2014;100:11-7.
96. NHS Blood and Transplant. (2013). National comparative audit of blood transfusion. [online] Available from <http://hospital.blood.co.uk/audits/national-comparative-audit/>. [Accessed November, 2016].
97. Rothschild JM, McGurk S, Honour M, et al. Assessment of education and computerized decision support interventions for improving transfusion practice. *Transfusion*. 2007;47:228-39.
98. American College of Physicians: Practice strategies for elective RBC transfusion. *Ann Intern Med*. 1992;116:403-6.
99. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: An updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006;105:198-208.
100. Scottish Intercollegiate Guidelines Network (SIGN). Perioperative blood transfusion for elective surgery. A national clinical guideline. Edinburgh (Scotland): SIGN Publication; 2011. p. 54.
101. Scottish Intercollegiate Guidelines Network (SIGN). Perioperative blood transfusion for elective surgery. Update to printed guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004.
102. Canadian Medical Association Expert Working Group. Guidelines for RBC and plasma transfusion for adults and children: Report of the Canadian Medical Association Expert Working Group. *Can Med Assoc J*. 1997;156:S1-24.
103. West MA, Shapiro MB, Nathens AB, et al. Guidelines for transfusion in the trauma patient. Inflammation and the host response to injury, a large-scale collaborative project: Patient-oriented research core—Standard operating procedures for clinical care. *J Trauma*. 2006;61:436-9.
104. The Society of Thoracic Surgeons Blood Conservation Guideline Task Force. The Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion: Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline. *Ann Thorac Surg*. 2007;83:S27-86.
105. Westbrook A, Pettilä V, Nichol A, et al. Blood Observational Study Investigators of ANZICS-Clinical Trials Group. *Intensive Care Med*. 2010;36:1138-46.
106. Goodnough LT, Murphy MF. Do liberal blood transfusions cause more harm than good? *BMJ*. 2014;349:g6897.
107. Tinagat H, Chattree S, Iqbal A, et al. Ten-year pattern of red blood cell use in the North of England. *Transfusion*. 2013;53:483-9.
108. Tinagat H, Pendry K, Murphy M. Where do all the red cells go? Results of a survey of red cell use in England and North Wales in 2014. *Transfusion*. 2015;56:139-45.
109. Mirski MA, Frank SM, Kor DJ, et al. Restrictive and liberal red cell transfusion strategies in adult patients: reconciling clinical data with best practice. *Critical Care*. 2015;19:202.

Section 8

Quality

SECTION EDITOR: PRADEEP RANGAPPA

Post-intensive Care Unit Syndrome

Vignesh C, Raymond D, Ramakrishnan N

INTRODUCTION

Advances in the management of the critically ill have resulted in an increase in the number of post-intensive care unit (ICU) survivors. Many of these patients are at risk of developing impairment in various domains such as physical function, mental health, and cognition, which can be severe enough to impair their quality-of-life. The family members of these individuals are also likely to suffer from some of these psychosocial issues. While this may be a transient phenomenon in a few, it may be long lasting and sometimes even permanent in others. Awareness of these challenges is essential for the critical care provider in order to perform an early assessment, to promptly identify and mitigate the risk factors, to document predischarge functional status, to educate the patient, family and the post-ICU care providers, and more importantly to develop an appropriate patient centered discharge and follow-up plan for better long-term outcomes.

DEFINITION

The Task force of the Society of Critical Care Medicine (SCCM) defines post-ICU care syndrome (PICS) as a new onset dysfunction or worsening function persisting beyond acute care hospitalization. This may involve one or more of the three domains, namely, cognition, psychiatric, and physical function. This term applies to ICU survivors (PICS) as well as to their families (PICS-F).¹ The term PICS-F denotes the effect of critical illness on the psychological health of the patient's family members. Most of these manifestations can be identified immediately after ICU/hospital discharge. However, the exact time of onset to define PICS after critical illness has not been established.

EPIDEMIOLOGY

Among the estimated 5.7 million annual ICU admissions in the United States, 4.8 million survive and more than half

of the patients develop dysfunction in one of the domains of post-ICU syndrome. There is wide variability in the incidence of cognitive impairment reported among the ICU patients. This variability is due to the difference in the study population, admission diagnosis and the assessment tool used. The studies, which used a questionnaire or screening-based assessment, reported 10% patients to have cognitive impairment whereas the studies that used standard neuropsychological testing noted 45–80%.² The incidence is higher among patients recovering from acute respiratory distress syndrome (ARDS). The brain ICU study reported a 6% incidence of cognitive impairment at discharge, 40% had impairment similar to moderate traumatic brain injury at 3 months and 26% had impairment similar to mild dementia. The deficits persisted at 12 months in most of the patients.³

The prevalence of post-traumatic stress disorder (PTSD) also differed among different studies (5–64%) based on the timing of evaluation, the population that was studied and the assessment methods. The existing data indicate that PTSD is relatively common among ICU survivors and symptoms persist for many months after recovery from critical illness.⁴

The median prevalence of clinically significant depressive symptoms post-ICU discharge was 22% whereas the point prevalence 2 months post-ICU discharge was 33%. Also, there is significant decrease in depressive symptoms during the first 2–12 months post-ICU discharge.⁵

The incidence of ICU-acquired weakness is 26–65% after 5–7 days of mechanical ventilation and it persisted in >25% after 7 days. It occurs in 67% of patients having long-term ventilation (>10 days). The incidence is higher among ARDS patients and it persisted in 36% of the patients at the time of discharge.

ETIOLOGY AND RISK FACTORS

The neurocognitive affliction and recovery of ICU survivors depends on a multitude of factors including age, prior neurocognitive function, genetic factors, comorbidities, nature of critical illness, secondary insults and so on. Among

the nonmodifiable risk factors, a female gender and younger age appear to influence the development of PTSD. One of the major modifiable risk factors, which can significantly worsen cognitive function, is ICU delirium apart from memories of "horrible delusions," recall of actual painful physical experience and traumatic procedures during ICU stay.⁶ Lack of ICU sedation policy and more interestingly, the use of benzodiazepines (especially, cumulative dose), neuromuscular blockers and modulators of adrenal axis are associated with an increased risk for cognitive dysfunction. Patients with coexisting psychiatric morbidity including anxiety, depression and PTSD, or those presenting with traumatic brain injury understandably have a higher incidence of post-ICU cognitive dysfunction. The presence of some of the common comorbidities such as hypertension, atrial fibrillation, cerebral, and coronary vascular disease has also been shown to contribute to cognitive dysfunction. Needless to say, the secondary insults incurred during ICU stay, viz., hypoxia, hypoglycemia, ARDS, and severe sepsis can also pave way for cognitive dysfunction as a sequel to neuronal injury. Severity of illness and length-of-stay in hospital are not shown to be associated with an increased risk for PTSD.²

The occurrence of post-ICU anxiety/depressive illness appears to be influenced by the pre-ICU physical and psychopathic functional status, poor recall of ICU events, memories of nightmares and fearfulness in ICU, depressive symptoms at hospital discharge, post-ICU PTSD, nonspecific anxiety symptoms, and post-ICU physical function. Other factors such as age, sex, admission diagnosis, severity of illness, length-of-stay in ICU, and ICU sedation have not been shown to consistently correlate with significant post-ICU depressive symptoms.⁵

As for post-ICU weakness, this is usually from critical illness myopathy, neuropathy, or both. The risk factors associated with physical decompensation in the post-ICU period additionally include old age, ARDS, duration of mechanical ventilation, sepsis, glucose dysregulation during ICU stay, steroid therapy, and usage of neuromuscular-blocking agents. Patients recovering from critical illness also have a high incidence of malnutrition, which can further impair physical function. Critical illness-associated peripheral nerve palsies, and sensory disturbances, dysphagia, change in taste, stiff frozen joints, pressure sores, scars from central lines and other devices, striae from volume overload, tracheal stenosis, cosmetic issues, and surgeries performed have a profound impact on the physical and mental health.⁷

PATHOPHYSIOLOGY

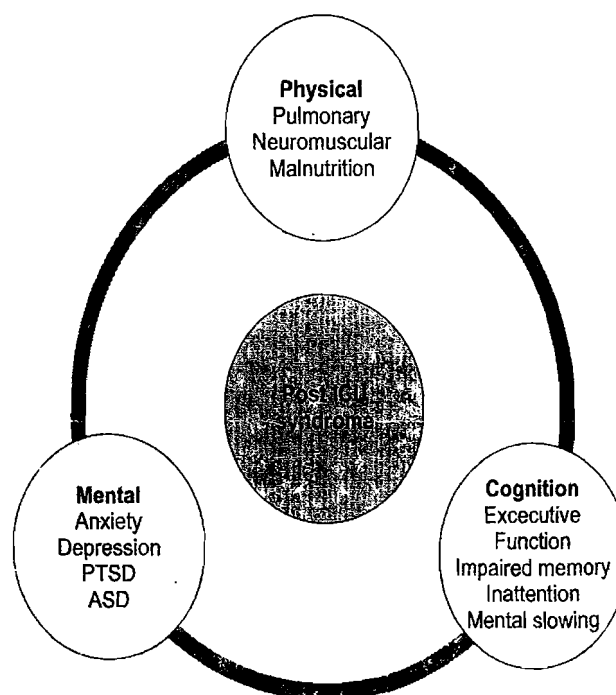
The basic pathophysiology for the cognitive and psychological impairment is poorly understood. It is highly complex and probably multifactorial involving the interaction of various systems. The common mechanism for cognitive and psychological impairment is injury to specific areas of the brain involved in executive functions like hippocampus and

prefrontal cortex by ischemia, hypoxia, glucose dysregulation, inflammation, disruption of blood brain barrier, white matter changes, etc.² The involvement of frontal cortex results in typical dysexecutive syndrome.⁸ This executive area forms the interface between the long-term memory and several organs, which coordinate information and execute functions. The impairment of physical function may be from any of the factors already discussed and their respective mechanisms.

All the three domains are interdependent and impairment in any domain can adversely affect the others. There is likely to be a "looping effect".² For example, post-ICU depression may result in low motivation with poor effort causing psychomotor slowing subsequently affecting cognition. Patients with depression can also refute active participation in physical rehabilitation programs. Likewise, patients with poor physical function are more prone for psychiatric morbidity and ultimately limiting their cognitive abilities (Fig. 1).

PRESENTATION

Patients recovering from critical illness may present with dysexecutive syndrome characterized by impairment in memory, problem-solving skills, and social decision making. There is an inability to form and execute a plan due to impaired attention and concentration, likewise there is inability to process available information due to impaired memory and mental slowing. Increased episodes of absent-mindedness and slip of actions are also very prominent.



ICU, intensive care unit; PTSD, post-traumatic stress disorder; ASD, acute stress disorder.

FIG. 1: Post-intensive care unit syndrome: The diagram shows the individual components of each domain affected in post-intensive care unit syndrome. The impairment in one domain affects other domain exhibiting a looping effect

Acute PTSD should be considered if the symptoms persist for 1 month after the stressor event, whereas chronic PTSD is diagnosed when symptoms persist for >3 months after discharge. Another entity called delayed onset PTSD can occur, if symptoms start 6 months after the stressor event. The usual manifestations of PTSD are intrusive recollections (re-experiencing the trauma in flashback, memories, and nightmares), avoidant and numbing symptoms (diminished emotions and avoidance of situations that remind of the experience), and hyperarousal (increased irritability, exaggerated startle reactions, or difficulty sleeping or concentrating).⁹ Post-traumatic stress disorder symptoms are also often associated with sexual dysfunction.

The patient with depressive symptoms usually complains of extreme fatigue, sense of hopelessness, loss of interest, insomnia, and poor appetite. Common symptoms of anxiety include restlessness, irritability and sleeplessness.

Patients suffering from ICU-acquired weakness may present with nonspecific muscle weakness (varying degrees of tetraparesis or quadriparesis), loss of muscle mass, and/or sensory disturbances. The physical impairments are also complicated by development of contractures in major joints especially in knees, ankles and elbows. In patients recovering from ARDS and on prolonged ventilatory support, lung functions are also impaired as manifested by a decreased diffusing capacity of the lungs and reduced lung volumes. Sexual dysfunction secondary to underlying lack of desire, impotence, neuromuscular weakness, and impaired cardiopulmonary function has been reported to occur in 44% of the patients.¹⁰

EVALUATION

A high index of suspicion is essential for the diagnosis of PICS. All survivors of critical illness should be screened for the signs and symptoms of PICS.

Timing

Baseline assessment of all the three domains should be done at the time of ICU discharge and discharge from hospital. This should be repeated 3–6 months after hospital discharge to allow for recovery of transient impairments. From then on, the assessments need to be repeated at regular intervals as warranted according to the clinical situation of the patient.¹¹

Evaluation of the cognitive domain in this patient group is likely to be challenging. These tests should be highly sensitive and have to be simple enough to be completed in less time. Factors to be considered for selecting an appropriate test are length of administration time, sensitivity, reliability, floor and ceiling effects, alternate parallel forms, and availability of normative data. The commonly used screening tests are Mini-Mental state examination, the Mini-Cog test, and

Montreal cognitive assessment scale. Among these tests, the Mini-Cog test is simple and takes less time to complete. The Montreal cognitive assessment scale is highly sensitive and predominantly tests executive functions. There are also tests available for assessing individual domains of cognitive function. For example, Wisconsin card sorting test measures the executive function whereas Block design measures the visual spatial construction. However, none of these tests are validated in ICU patients.¹¹

To diagnose cognitive decline, we need to have information on the baseline neuropsychological condition of the patient, which needs to be assessed prior to ICU admission. It has been demonstrated that adult children and spouse are highly reliable observers and can detect even subtle changes in the neurocognition of their loved ones. To diagnose the preadmission baseline neurocognitive status, informant-based questionnaires are mostly used such as informant questionnaire on cognitive decline in the Elderly and the Modified Blessed Dementia-rating Scale.¹²

Post-traumatic stress disorder diagnosis should be based on a combination of self-reported inventories and standardized clinical interview. The common self-reported inventories used to assess symptomatology of PTSD are modified post-traumatic stress syndrome 10 questions inventory (PTSS-10), impact of event scale revised (IES-R), and Davidson trauma scale. The structured clinical interview for DSM-IV (SCID) and the clinician-administered PTSD scale (CAPS) are some of the standardized clinical interview-based diagnostic tools available for accurate diagnosis for PTSD.⁴

Depressive symptoms are measured by structured clinical interview for DSM-IV, which is a structured psychiatric diagnostic interview conducted by a clinician. Other commonly used tools are Beck Depression Inventory II, the Hospital Anxiety and Depression scale, the Centre for Epidemiological Studies depression scale, and Geriatric Depression rating scale—short form.^{12,13}

Similarly, the Beck anxiety inventory, Hospital Anxiety and Depression scale, and Zung's anxiety tool are commonly used to assess anxiety symptoms in post-ICU survivors.^{13–15}

The assessment for physical health should be done while the patient is in the ICU by trained personnel (physiotherapist) to identify the ones at risk of developing ICU-acquired weakness. It should also be evaluated at the time of discharge and at frequent intervals postdischarge in the follow-up/rehabilitation clinic. For those suspected to have ICU-acquired weakness, formal assessments with nerve conduction study and electromyography should be done.¹⁶ In patients recovering from ARDS and on prolonged mechanical ventilation, pulmonary function test should be done when feasible to determine the residual lung function in the post-ICU period and to track improvement. Exercise tolerance should be assessed with standard 6-minute walk test and handgrip dynamometer¹⁷ (Table 1).

TABLE 1 Commonly used assessment tools for the diagnosis of post-intensive care unit syndrome

Domains	Assessment tool
Cognition	<ul style="list-style-type: none"> • Mini-Mental state examination • Mini-Cog test • Montreal cognitive assessment scale • Informant questionnaire on cognitive decline in the elderly • The Modified Blessed Dementia-rating scale
Post-traumatic stress disorder	<ul style="list-style-type: none"> • Modified post-traumatic stress syndrome 10 questions inventory (PTSS-10) • Impact of event scale revised (IES-R) • Davidson trauma scale • The Structured Clinical Interview for DSM-IV (SCID) • The Clinician-Administered PTSD Scale (CAPS)
Anxiety	<ul style="list-style-type: none"> • Beck anxiety inventory • Hospital Anxiety and Depression Scale • Zung's anxiety tool
Depression	<ul style="list-style-type: none"> • Structured clinical interview for DSM-IV • Beck depression inventory II • The Hospital Anxiety and Depression scale • Center for Epidemiological Studies depression scale • Geriatric Depression rating scale—short form
Physical	<ul style="list-style-type: none"> • Pulmonary function test • 6-minute walk test • Hand grip dynamometer

DSM-IV, diagnostic and statistical manual of mental disorders—4th edition; PTSD, post-traumatic stress disorder.

PREVENTION AND TREATMENT

Post-ICU syndrome usually has a prolonged course and may often be permanent making it prudent to adopt whatever preventive strategies feasible. The most discussed strategy is to minimize sedation and promote early mobilization. An ABCDEFGH bundle approach is recommended in mechanically ventilated patients to prevent PICS¹ (Box 1).

The impact of light sedation, daily sedation interruptions, and spontaneous-breathing trials in improving outcomes has been proven beyond doubt. Limiting the dose of

sedation and avoidance of benzodiazepines reduces the risk of delirium in ICU patients. Intensive care unit delirium is the major risk factor for neurocognitive impairment and is hence essential to systematically monitor for delirium with Confusion Assessment Method for the ICU (CAM-ICU) score. Delirium risk can be mitigated with “STOP, THINK, MEDICATE” strategy. It includes stopping sedation and other medication, which can contribute to delirium and to correct risk factors for delirium including toxic conditions, hypoxemia, infection, and electrolyte imbalances, to mention a few. Nonpharmacological interventions like providing hearing aids, goggles as required, reorienting frequently, sleep protocols, music, noise control, and early ambulation can reduce the incidence of delirium as well. Medication such as atypical antipsychotics and dexmedetomidine can be used, where appropriate, to mitigate symptoms of delirium.¹⁸

Intensive care unit-based early mobility program, in addition, has been shown to improve the recovery from functional impairment, which is usually slow to resolve and poorly responding to rehabilitation programs rendered postdischarge. Involving the rehabilitation services and including a physiotherapist early during ICU stay could promote the development of a plan for early and safe mobility, which can improve physical abilities and limit loss of function and disability that otherwise occur in the critically ill.¹⁹

Functional reconciliation involves systematic assessment of the functional status of the patient and comparing their current status with prehospitalization functional status. This will enable in identifying the patient at risk of developing PICS and to initiate appropriate interventions aimed at limiting disability.¹

It is imperative to have good communication among the various members of the team involved in patient care. The detailed postdischarge plan including medical, physical and cognitive rehabilitation therapy should be discussed among all the team members and it should be clearly communicated during transition of care to the subsequent caring team in order to maintain continuum of care. The follow-up team providing postdischarge care is often unaware of issues pertaining to the period of critical illness and it becomes necessary to educate them regarding the same and the likelihood of a PICS.

Survivors of critical illness are usually discharged without a formal briefing/training regarding their illness and postdischarge requirements. Neither are the family members informed of the events that are likely to follow and the strategies to cope up with and manage these issues. Hence, the critical care survivor and the family members should be provided formal information regarding post-ICU discharge course including the possibility of a physical, cognitive, and mental impairment and its outcomes. Educating the family members and the patients, starting from ICU stay to postdischarge, with various modalities like printed educational materials and videos has consistently shown to

Box 1: ABCDEFGH bundle approach

- Awakening with Breathing Coordination with daily interruption of sedation and SBT
- Delirium monitoring and management
- Early ambulation in ICU
- Functional reconciliation
- Good handoff communication
- Hand-written family information

ICU, intensive care unit; SBT, spontaneous breathing trial

reduce the level of anxiety and PTSD among patients and their family.²⁰

Intensive Care Unit Diaries

An ICU survivor's mental health depends on the memories of not only the actual events that occurred during ICU stay but also his delusions. Intensive care unit diaries are documents of the real experience of ICU events written by whoever visits the patient (nurse, doctor, physiotherapist, family members or other ancillary service providers) mentioning their interaction with the patient during ICU stay.²¹ This is to be transferred along with the ICU patient and the documentation is to be continued. Such diaries will help the patient overcome factual memories and misconceptions developed during ICU stay. It helps the patient to make sense of his experience in the ICU. It is a low-cost strategy shown to improve the quality-of-life after discharge.²² It also helps as a source of inspiration for the patients and their families and helps them to cope with difficult circumstances in the ICU.

Post-intensive Care Unit Clinic

Post-ICU clinics are helpful in identifying the special needs of the critical care survivors and help in their rehabilitation. It is aimed to provide the survivors with the information needed and the expected course of recovery. It involves a multidisciplinary team approach including a critical care physician, registered nurse, social worker, physical therapist, psychometrician, psychologist, psychiatrist, and clinical dietician. There are various models available for providing post-ICU follow-up clinics. The most comprehensive model for post-ICU clinic was formulated by British National Institute for Clinical Excellence. These clinics are meant to address the neurocognitive and psychological sequel in addition to performing routine disease-specific follow-up. Existing data show a trend to improvement in PICS when patients were followed up at a post-ICU clinic; however, this did not translate to improved quality-of-life.²³

Peer Support Group

The survivors and their care givers have the best experience of the challenges faced during recovery. They are best placed to educate and prepare other survivors for recovery. Peer support group is a process of providing empathy, advice, and sharing stories between ICU survivors and their care givers, which is expected to promote mental reframing, information sharing, effective modeling, and also to provide practical advice that is not routinely available from healthcare providers. The participation should be voluntary and with mutual respect. The clinician's role is to arrange a suitable place and time convenient to all. Engaging facilitators to moderate the meeting may improve the outcomes of such a meeting.²⁴

Cognitive Therapy

Cognitive therapy, aimed at training the patient to identify and correct distorted beliefs and behavioral therapy involving thought exercises and real experiences, has been shown to improve executive function.²⁵ However, the efficacy of early cognitive therapy to prevent PICS is not known.

OUTCOME

The symptoms of the components of PICS improve gradually over 6 months to 1 year postdischarge. However, many patients can persist to have varying deficits for years, impairing their quality-of-life. Cognitive impairment, anxiety, PTSD, and depression are shown to persist for years postdischarge. The effects of these impairments in terms of rehospitalization, mortality and recurrence of PICS are not known.

Health-related quality-of-life is a global outcome measure found most appropriate for ICU survivors and care givers. It is profoundly influenced by age, premorbid health status, and expectation to return to premorbid functional status. Low scores are noted in patients post-ARDS, mechanical ventilation, sepsis, trauma, and malignancy.⁷

The risk of rehospitalization is high among survivors of critical illness. Twenty five percent of the patients are at risk of readmission to hospital within the first month postdischarge. The factors associated are severity of illness, malignancy, and patients discharged to skilled care facility. Mortality rate is high in the initial 3–6 months from ICU admission and is related to the severity of illness, new impairments, and new or worsening organ dysfunction.

POST-INTENSIVE CARE UNIT SYNDROME—FAMILY

The family members of the critically ill patients are also at a profound risk for psychological dysfunction. The usual manifestations of PICS-F are anxiety, depression, major stress disorder, PTSD, and complicated grief. The median prevalence derived from various studies for clinically significant PTSD, anxiety, and depression among the family members are 35%, 43%, and 22%, respectively.²⁶

The risk factors for PICS-F are young age, absence of chronic disease, severity of illness and death (patient related), female gender, young relative, lower educational level, prior history of psychiatric illness, spouse, decision maker (family related) and communication by the critical care team, and absence of waiting room (care process related).

Post-ICU syndrome—family is frequently diagnosed by self-reported questionnaires. Post-traumatic stress disorder is frequently assessed by the Impact of Event Scale whereas anxiety and depression is assessed by Hospital Anxiety and Depression Index. None of these tools have been validated.

Various strategies have been tried and studied to reduce the psychological burden of the family of the critically ill

patient. Proactive and effective communication helps the family to anticipate and prepare themselves for the possible events in the ICU. Providing information in various formats (printed materials and videos) has been shown to be effective in aiding the family to participate in treatment decisions. Conducting frequent nurse-physician meeting with the family providing separate room for counseling, proper waiting room for the family and having a flexible visiting time have all been shown to reduce the anxiety and psychological stress of the family. Involving a nurse family-care specialist further improved the psychological status of the relative by establishing liaison between the critical care team and the relatives. Making family members participate in care of the patient (facilitated sense making) also makes better the decision-making process for the family and prepares them for future care-giving role.²⁷

Post-ICU discharge strategies like family debriefing visits and post-ICU family follow-up clinics may additionally be helpful in reducing the psychological burden of patients after discharge. However, the existing studies have not shown such strategies to reduce the risk of depression among family members.

CONCLUSION

Post-ICU syndrome is a symptom complex being increasingly identified in survivors of critical illness. The individual components, namely, neurocognitive dysfunction, psychiatric illness, and physical limitation including organ systems and sexual dysfunction have been shown to have a tremendous impact on quality-of-life of patients posthospital discharge. A lot remains to be understood about the complex etiopathogenesis of this rather intimidating long-term complication of acute illness and therefore its care. While several tools are available for early assessment and identification of this problem, none have been validated or proven to have an impact on outcomes. Following evidence-based standard operating procedures having a high index of suspicion for likely PICS and advance planning for the rehabilitative period seem to be favorable strategies in ameliorating the severity of PICS. Needless to say, a complete understanding of all risk factors involved is mandatory and the development of a PICS-oriented "bundle" approach would be a more welcome measure. A more sympathetic approach to the family of the critically ill additionally seems to be of paramount importance in not only making better the care of patients but also in preventing PICS-F. The role of post-ICU follow-up clinics is being better appreciated of late as an important means of providing an all-round care for the post-ICU patients with special requirements, which are better understood by the critical care team.

REFERENCES

- Needham DM, Davidson J, Coher H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med.* 2012;40:502-9.
- Skrobik Y, Hopkins RO. Post-intensive care cognitive impairment: questions in mind? *Intensive Care Med.* 2013;39:524-7.
- Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369:1306-16.
- Griffiths J, Fortune G, Barber V, et al. The prevalence of post-traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med.* 2007;33:1506-18.
- Davydow DS, Gifford JM, Desai SV, et al. Depression in general intensive care unit survivors: a systematic review. *Intensive Care Med.* 2009;35:796-809.
- Misak C, Hopkins R, Brett S, et al. Cognitive dysfunction after critical illness: measurement, rehabilitation, and disclosure. *Crit Care.* 2009;13:312.
- Herridge MS. Long-term outcomes after critical illness: past, present, future. *Curr Opin Crit Care.* 2007;13:473-5.
- Jones C, Griffiths RD, Slater T, et al. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Med.* 2006;32:923-6.
- Long AC, Kross EK, Davydow DS, et al. Posttraumatic stress disorder among survivors of critical illness: creation of a conceptual model addressing identification, prevention, and management. *Intensive Care Med.* 2014;40:820-9.
- Griffiths J, Gager M, Alder N, et al. A self-report-based study of the incidence and associations of sexual dysfunction in survivors of intensive care treatment. *Intensive Care Med.* 2006;32:445-51.
- Jackson JC, Gordon SM, Ely EW, et al. Research issues in the evaluation of cognitive impairment in intensive care unit survivors. *Intensive Care Med.* 2004;30:2009-16.
- Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol.* 1988;56:893-7.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361-70.
- Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-71.
- Biggs JT, Wylie LT, Ziegler VE. Validity of the Zung Self-rating Depression Scale. *Br J Psychiatry.* 1978;132:381-5.
- Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med.* 2014;370:1626-35.
- Ali NA, O'Brien JM, Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med.* 2008;178:261-8.
- Stollings JL, Bloom SL, Huggins EL, et al. Medication management to ameliorate post-intensive care syndrome. *AACN Adv Crit Care.* 2016;27:133-40.
- Bemis-Dougherty AR, Smith JM. What follows survival of critical illness? Physical therapists' management of patients with post-intensive care syndrome. *Phys Ther.* 2013;93:179-85.
- Carson SS, Vu M, Danis M, et al. Development and validation of a printed information brochure for families of chronically critically ill patients. *Crit Care Med.* 2012;40:73-8.
- Locke M, Eccleston S, Ryan CN, et al. Developing a diary program to minimize patient and family post-intensive care syndrome. *AACN Adv Crit Care.* 2016;27:212-20.
- Egerod I, Christensen D, Schwartz-Nielsen KH, et al. Constructing the illness narrative: a grounded theory exploring patients' and relatives' use of intensive care diaries. *Crit Care Med.* 2011;39:1922-8.
- Jensen JF, Thomsen T, Overgaard D, et al. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. *Intensive Care Med.* 2015;41:763-75.
- Mikkelsen ME, Jackson JC, Hopkins RO, et al. Peer support as a novel strategy to mitigate post-intensive care syndrome. *AACN Adv Crit Care.* 2016;27:221-9.
- Jackson JC, Ely EW, Morey MC, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Crit Care Med.* 2012;40:1088-97.
- Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. *Crit Care Med.* 2012;40:618-24.
- Ploot G, Nelson D. Family care in the intensive care unit: the Golden Rule, evidence, and resources. *Crit Care Med.* 2007;35:669-70.

End-of-life Care of Intensive Care Units in Asia: Ethical Aspect

Younsuck Koh

INTRODUCTION

We, as intensivists, know how patients die in our hospital. Ironically, we frequently do not know well how our patients wish to die. It is relatively easy for intensivists to provide more treatment than to know when to stop in a critically ill patient. End-of-life (EOL) care is a medical care provided in final period of a person's life usually requiring decisions on withholding and/or withdrawal of life-sustaining therapy (LST). Maintaining unresponsive intensive care but prolonging dying process leads to patients' and their families' unbearable suffering and financial burden. A study revealed that many patients, who died under mechanical ventilation support were receiving unwanted painful LST.¹ As painful EOL experience for a loved one remains in his or her relatives' memory, the EOL care should be carefully prepared in advance and performed well in intensive care units (ICUs). As we are moving rapidly towards aged society, appropriate comfort care for terminally ill patients becomes a sensitive and urgent issue in Asia. Fair resource allocation under limited medical resources is another hidden big issue of EOL care in Asia. This article aims to review current status and to discuss relevant ethical issues of EOL cares in Asian countries.

SHIFTING FROM CURE TO COMFORT CARE

When there are no reasonable treatments beneficial to critically ill patients, physicians should change the aim of management from cure to comfort care. Comfort care aims to relieve unnecessary suffering and humane care for patients and their families. Do-not-resuscitate (DNR) order at cardiac arrest or do-not-intubate is a typical example of comfort care. Ethical and emotional problems can arise when a caregiver judges withhold or withdraw certain care to be without medical and ethical certainty. It sometimes brings a futility debate between patient's family and caregivers when

the family insists to continue or discontinue intensive cares against caregivers' advice. Futility is a value-laden term, which has been frequently used in medical societies. It would be better to avoid saying "futile" in EOL care discussions at a patient bedside, because there is no consensus on the definition of futility.² A practice policy of EOL care issued by the Indian Society of Critical Care Medicine provides a guideline to recognize medical futility (Box 1).³ Moreover, the guideline also recommended that these medical futility points should not be used in isolation without considering underlying medical context of the patient.³ Instead, it would be better to use a descriptive term such as "unresponsive".

The common difficulty in timely shifting from cure to palliative care is the unpreparedness for a death in both the patient's family and caregivers. Very few patients have advance directives (AD) or clear decision for their

Box 1: Recognizing medical futility³

- Advanced age coupled with poor functional state due to one or more chronic debilitating organ dysfunction. For example, end stage pulmonary, cardiac, renal, or hepatic disease for which the patient has received/declined standard medical/surgical options
- Severe refractory illnesses with organ dysfunctions unresponsive to a reasonable period of aggressive treatment
- Coma (in the absence of brain death) due to acute catastrophic causes with nonreversible consequences such as traumatic brain injury, intracranial bleeding, or extensive infarction
- Chronic severe neurological conditions with advanced cognitive and/or functional impairment with little or no prospects for improvement. For example, advanced dementia, quadriplegia, or chronic vegetative state
- Progressive metastatic cancer where treatment options have failed
- Post cardiorespiratory arrest with prolonged poor neurological status
- Any other comparable clinical situations coupled with a physician prediction of low probability of survival

EOL cares when admitted to ICUs. Advance directives are statements expressed by competent individuals for their medical preferences in the event of becoming incapacitated. Advance directives have a binding force in EOL care practice by an explicit expression of patient's autonomy. As patient's preference can change over time, physician should reconfirm the AD of a patient when a relevant medical situation arises.

Physicians should play a central role to forgo treatments that are not beneficial to a patient. However, physicians are not allowed to make unilateral decision on EOL care in most countries. Current medical ethics and legal requirements ask physicians to make a shared decision respecting patient autonomy. In current medical ethics, respect for patient autonomy is considered as the utmost value. Limiting LST can be justified under the principle of autonomy.⁴

HOW IS IT DIFFERENT IN ASIAN INTENSIVE CARE UNITS?

The difficulty to make an EOL care decision relies on diverse situations and factors associated with individual patients. Multiple factors related to country or region, including economic, cultural, religious, and legal differences, as well as personal attitudes, were associated with different EOL care level in Asian ICUs. We conducted intensive care

physicians' perception of EOL care in 466 ICUs of 16 Asian countries/regions. About 1,465 physicians, who manage patients in ICUs, participated in the survey.⁵ As expected, there was a huge diversity of doctors' views on EOL care across Asia. For patients with no real chance of recovering a meaningful life, 1,029 respondents (70.2%) reported almost always/often withholding, while 303 (20.7%) reported almost always/often withdrawing life-sustaining treatments. The majority of respondents reported that mechanical ventilation, vasopressors, hemodialysis, and antibiotics could usually be withheld or withdrawn in EOL care, but not enteral feeding, intravenous fluids, and oral suctioning. In a hypothetical setting of hypoxic-ischemic encephalopathy, the corresponding range to implement DNR order was 48.4–100% among the respondents. For severe hypoxic-ischemic encephalopathy post cardiac arrest, 1,201 respondents would implement DNR orders, but 788 would maintain mechanical ventilation and start antibiotics and vasopressors if required. These proportions varied widely among Asian ICUs (Fig. 1), and physicians in Asian ICUs seemed to be less likely to limit life-sustaining treatments at the end of life than Western physicians in a similar survey.⁶ Refusal to implement DNR order was independently associated with physicians who did not value families' or surrogates' request, were uncomfortable discussing EOL, perceived greater legal risk, and in low-to middle-income economies.⁵

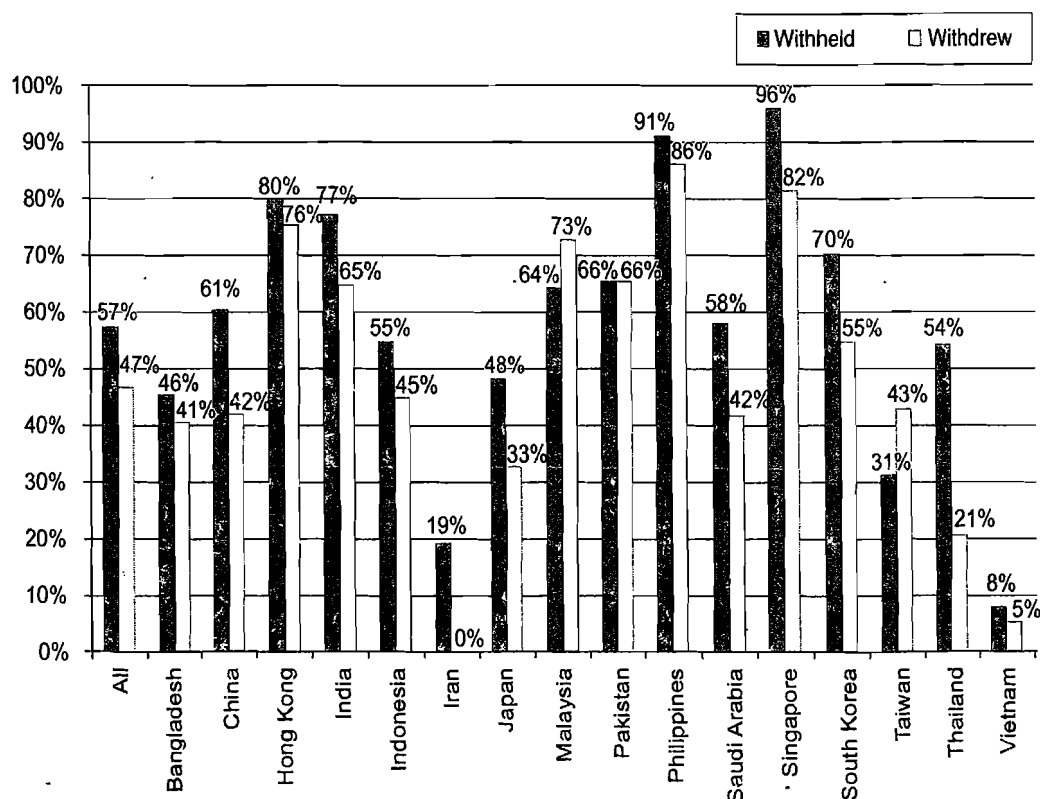


FIG. 1: Proportion of respondents by country who strongly agreed or agreed that mechanical ventilation can usually be withheld or withdrawn as part of limitation of life-sustaining therapy in end-of-life care.⁵

MAJOR ISSUES IN END-OF-LIFE CARE

Surrogate Decision Power

Patients want to know their status and prognosis. The patients' right to refuse unwanted medical intervention is well-established in Asia.⁵ Surrogate decision-making occurs when a patient does not provide direct input into a clinical decision. Familial input is strongly influential in Asian countries.⁵ However, it is unclear how to respect patient's family members' request to EOL care. If there were a healthcare proxy designated by the patient, the decision-making process could be done with the healthcare proxy. When no individual has been specifically designated, a predefined legal hierarchy in law for choosing a designated surrogate is an alternative. Physicians should be careful not to let surrogates to feel solely responsible for the withholding/withdrawal decision by merely providing treatments alternatives. Physician should identify clinically reasonable options and elicit the surrogate's sense of decision-making burden.

Ethical Differences between Withholding and Withdrawal of Life-sustaining Therapy

Most professional organizations have considered withholding and withdrawal of LST ethically equivalent, although there is a big difference between killing and allowing to die.⁴ In our previous study, 1,092 respondents (74.5%) among 1,465 physicians deemed withholding and withdrawal ethically different⁵ (Fig. 2). In another survey with speakers of an

International Intensive Care Congress in 2013, 16 among 20 respondents thought the withholding and withdrawal of LST ethically same.⁷ Allowing withdrawal of LST is considered an allowance to die by the underlying disease rather than the cause of the patient's death.⁴ In many cases of withholding LST, physicians frequently withhold information about treatments considered not beneficial to offer. No countries allow physicians' assisted dying in Asia. Physicians should not engage in physician-assisted suicide and euthanasia because this disrupts their endorsed role from their societies to heal and relieve the suffering of their patients.

Financial Burden

Although who pays a medical bill issue should not be a major barrier to make EOL care decisions from ethical point of view, financial burden seems to be one of key factors to influence an individual EOL care decision in Asia. Significant differences in ICU physicians' perceptions of various forms of life-sustaining treatments, the role of families and surrogates, legal risks, and financial considerations exist between low- and high-income Asian countries.⁸ Implementation of DNR for a patient with hypoxic-ischemic encephalopathy in a case scenario were less likely when out-of-pocket healthcare expenditure increased in Asian ICUs.⁵ Nonetheless, physicians from low-middle income countries were more likely to accede to families' requests to withdraw LST in a patient with an otherwise reasonable chance of survival on financial grounds in a case scenario.⁸ Pressure on family members to pay medical bills can frequently create an ethical

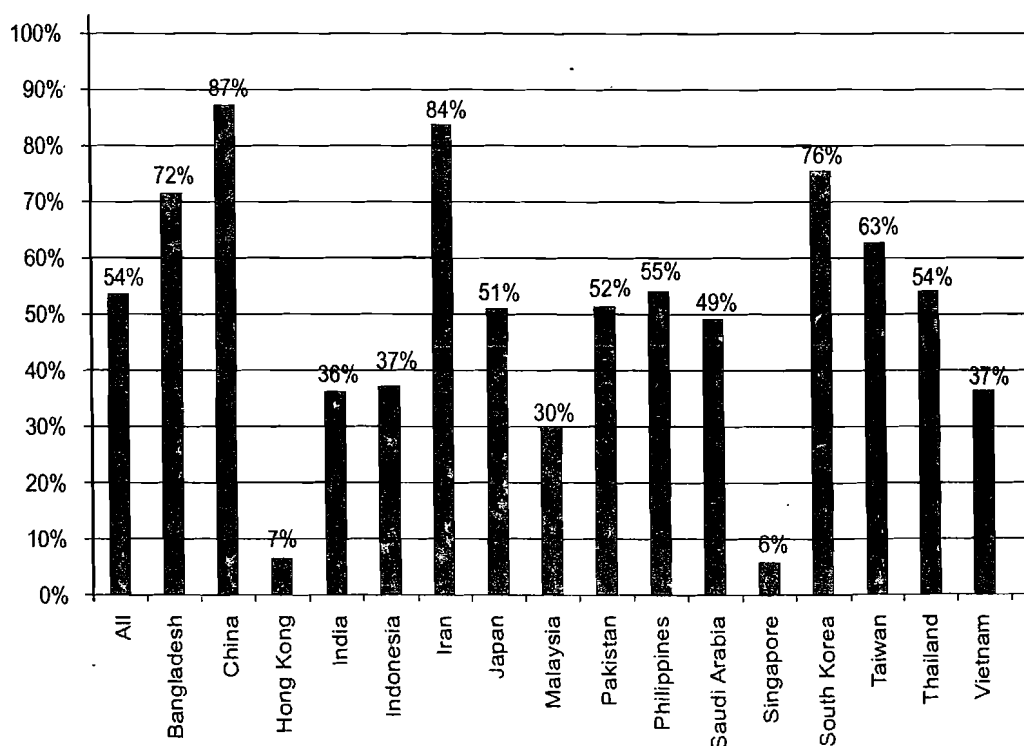


FIG. 2: Proportion of respondents by country who would maintain mechanical ventilation and start antibiotics and vasopressors for the patient with hypoxic-ischemic encephalopathy in the event of pneumonia with septic shock in case one.⁵

dilemma of physicians in low-middle income countries. Conflict between caregivers and family members over the level and nature of EOL care is often apparent when there is underlying financial burden.

Religious and Legal Issue

Physician's religion seems to affect EOL care. In our previous study, nonimplementation of DNR for terminally ill patients was less likely with physicians of Protestant and Catholic faiths.⁵ Families' religious belief also can influence EOL decisions of their patient. Legal concern related to the withholding/withdrawal of LST is also not well-addressed in most Asian countries. In many Asian countries, there are no formal laws recognizing ADs authority. Lack of clear legal guideline of EOL care in most Asian countries has been perceived as a major barrier to perform proper EOL care in Asia.⁵ Attending doctors should be careful not to violate legal guideline when to perform EOL care in their societies. Legal framework for LST decision has been highlighted whenever there is an exemplified law suit case drawing a hot debate in a society.

A Guideline for End-of-life Care

Wide variation in EOL care practices in Asia warrants consensus on the major relevant ethical principles. The relevant major ethical issues include informed consent, proxy power, shared decision-making process, respect for patient's autonomy, withholding and withdrawal of unresponsive LST, palliative care, and legal requirements. Although it is a sensitive matter to discuss freely in Asian countries, fair medical resource allocation is a big ethical issue in EOL care. End-of-life care has been reported to comprise a substantial portion of medical expense. It was over one-fourth of Medicare expenditures going to persons in their last year of life for elderly and has not been changed much despite changes in the delivery of medical care over the last decades in United States.⁹ The portion of EOL care in a national medical expenditure can be increased with the technological advance in sustaining life. However, it is difficult to reach social consensus to reduce avoidable medical expense related with prolonged EOL care practices. The wide variation in EOL care between critical care practitioners even in a same country requires policies for the EOL cares. However, any guideline to enhance EOL care in Asian ICUs may not be generalized across Asian ICUs. Instead, stepwise efforts to meet the encountered needs for better EOL cares should be pursued considering individual societies situations. The policies on EOL care should be clearly documented when prepared, and try to reach a consensus among medical societies, lay publics, and healthcare policy makers to be functionally operable in a society.

HOW TO APPROACH: ADVANCE CARE PLANNING THROUGH SHARED MEDICAL DECISION-MAKING

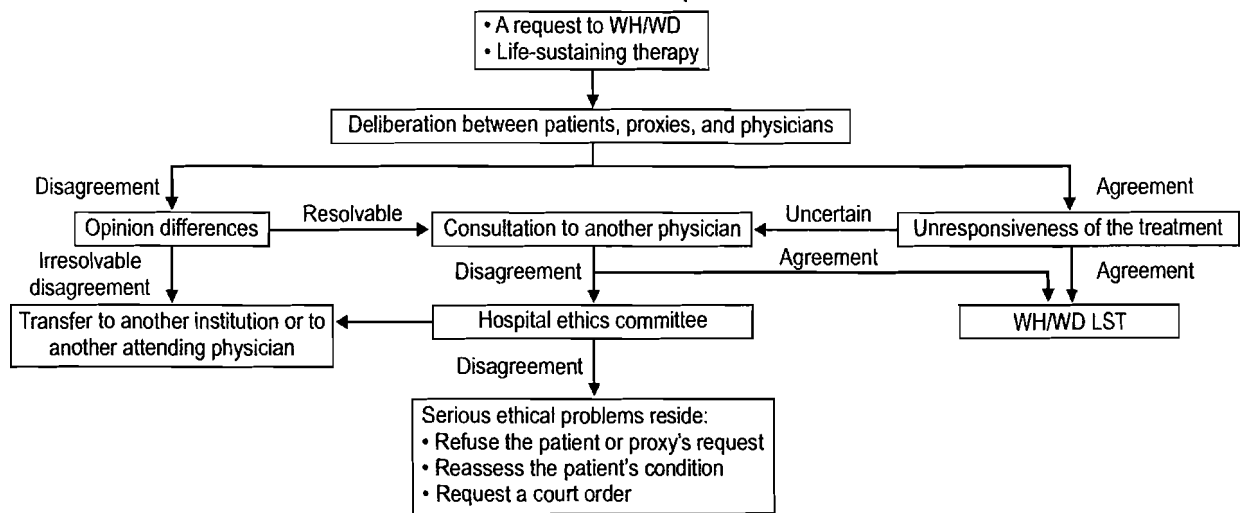
It is not usual and not easy to discuss EOL care with critically ill patients in advance in Asian ICUs. The ADs or medical orders for life-sustaining therapy (MOLST) is not a prevalent way to perform the EOL care in Asia. Patients and their families do not like to discuss about death in the early stages of intensive care. Hospital ethic committees do not seem to function well to cope with encountered EOL care issues at patient's bedside in most Asian countries. Under these barriers to appropriate EOL care decision-making, patient beneficence and autonomy may not have been carefully considered. In fact, discussions regarding patient preferences for resuscitation are frequently delayed leading to neglect of a patient's autonomy.

To overcome these barriers, role of attending physician is really significant. Identification of patients, who need a shifting critical care goal, is the first step of EOL care practices. Then, critical care management team should try to understand their patients' preference on EOL care through a communication with patients and their families. Information on a patient's preference can be exchanged through communications via speaking, writing, or using some other medium. Respect to counterpart is crucial to reach a consensus during an EOL care communication. Before communicating with patients and their relatives, consensus on advance care planning of LST should be made between all relevant caregivers through careful assessment of patient's clinical condition.

If there is uncertainty as to a patient's wishes, the management team should make a judgment to use measures that will neither prolong the patient's suffering nor unnaturally hasten the patient's death through an established algorithmic approach (Flowchart 1). A consensus guideline on EOL care endorsed by medical societies could be helpful to make a medical decision. Either overly burdensome by a prolonged LST or to loose a recovery opportunity is not in patient's best interests. End-of-life care is a major ethical burden also to critical care nurses.¹⁰ We found the ethical burden experienced by critical care nurses can be relieved by an on-site ethical consultation by a senior critical care physician.¹⁰

HOW TO EDUCATE CAREGIVERS AND COMMUNITY?

Huge cultural differences in views on EOL cares between low-, middle-, and high-income countries were observed in Asian intensive care providers. These differences may be observed in the lay public between Asian countries. As shared decisions through family conferences are crucial for meaningful EOL care, education of communication skill for caregivers is necessary.^{11,12} Sufficient communication



WH, withholding; WD, withdrawal; LST, life-sustaining therapy.

FLOWCHART 1: Algorithm for the decision process of withholding and withdrawal of life-sustaining therapy

with surrogates on EOL cares relieves stress and anxiety in family members.¹³ Better communications can be a good opportunity for family members to learn about a death in hospital. To enhance comfort care, education for a death should be initiated from an elementary school like United Kingdom. Medical societies should communicate with lay public and healthcare policy makers about how to enhance EOL care in our societies. A web based electronic system that guides clinicians, patients, and citizens is a way to address their inquiries and facilitate the discussions about EOL cares. One example is New York electronic MOLST for clinicians and patients, which is available statewide and can be access in their website (nysemolstregistry.com).

CONCLUSION

As many deaths occur through discontinuation of LST in ICUs, intensivists frequently face a situation to make decisions on a discontinuation of LST in a terminally ill patient. Lack of preparedness for death in not only critically ill patients and their families but also in critical caregivers frequently obstructs an optimal EOL care delivery. As expected, multiple factors related to country/region, including economic, cultural, religious, and legal differences, as well as personal attitudes were associated with variations in EOL cares in Asian ICUs. End-of-life care should be a planned and integrated care together with hospice care keeping personal dignity. Initiatives to improve EOL care in Asia must begin with a thorough understanding of each country's/region's culture, its physicians' attitudes, the prevailing ethicolegal framework, and healthcare funding. These initiatives to overcome financial and caring burdens of patients' families and relevant legal issues are urgently needed in most of Asian countries. Cultural change in our society about death in a hospital is also needed. The physicians should play a key role to enhance EOL care by

addressing these issues in our society together with medical and psychological issues of comfort cares.

REFERENCES

1. Investigators TSP. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA*. 1995;274:1591-8.
2. Burns JP, Truog RD. Futility: a concept in evolution. *Chest*. 2007;132:1987-93.
3. Myatra SN, Salins N, Iyer S, et al. End-of-life care policy: An integrated care plan for the dying: A Joint Position Statement of the Indian Society of Critical Care Medicine (ISCCM) and the Indian Association of Palliative Care (IAPC). *Indian J Crit Care Med*. 2014;18:615-35.
4. Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College [corrected] of Critical Care Medicine. *Crit Care Med*. 2008;36(3):953-63.
5. Phua J, Joynt GM, Nishimura M, et al. Withholding and withdrawal of life-sustaining treatments in intensive care units in Asia. *JAMA Intern Med*. 2015;175:363-71.
6. Yaguchi A, Truog RD, Curtis JR, et al. International differences in end-of-life attitudes in the intensive care unit: results of a survey. *Arch Intern Med*. 2005;165:1970-5.
7. Sprung CL, Paruk F, Kissoon N, et al. The Durban World Congress Ethics Round Table Conference Report: I. Differences between withholding and withdrawing life-sustaining treatments. *J Crit Care*. 2014;29:890-5.
8. Phua J, Joynt GM, Nishimura M, et al. Withholding and withdrawal of life-sustaining treatments in low-middle-income versus high-income Asian countries and regions. *Intensive Care Med*. 2016;42:1118-27.
9. Riley GF, Lubitz JD. Long-term trends in Medicare payments in the last year of life. *Health Serv Res*. 2010;45(2):565-76.
10. Park DW, Moon JY, Ku EY, et al. Ethical issues recognized by critical care nurses in the intensive care units of a tertiary hospital during two separate periods. *J Korean Med Sci*. 2015;30:495-501.
11. Levy MM. End-of-life care in the intensive care unit: can we do better? *Crit Care Med*. 2001;29:N56-61.
12. Bernacki RE, Block SD. Communication about serious illness care goals: a review and synthesis of best practices. *JAMA Intern Med*. 2014;174:1994-2003.
13. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. 2007;356:469-78.

Principles of Team Science in Intensive Care Unit

T Shyam Sunder, Nisha Tipparaju

INTRODUCTION

Team work is a cooperative or combined effort of a group of persons working together as a team for a common goal. Intensive care unit (ICU) working environment is very demanding and dynamic with small room for errors. This highly complex environment is associated with increased workload and work pressure on the multidisciplinary team. In order to perform comprehensively in a well-coordinated manner a team of highly trained and skilled workers are needed. Research from both management and medicine has consistently advocated effective team-based working as the optimal work method in healthcare settings. It is the team, which functions as a unit of administration in critical care and not the physician hence team dynamics do have an impact on outcomes. However, having a structured team in a critical care unit does not ensure improved outcomes.

There are three behavioral science concepts that have positive effect on the performance of team, psychological safety, transactive memory and leadership. These concepts when imbibed into daily practice will ensure an enhanced care.

CONCEPT OF TEAM SCIENCE

Cultivate Psychological Safety

In health care, like other industries, psychological safety plays an important and a crucial role in whether people with varied expertise and a huge difference in status—which are ascribed to healthcare teams—facilitate or disrupt team effectiveness. The term psychological safety refers to whether an individual's working environment is conducive to behavioral patterns that encourage the habit of asking questions, to seek help if needed, to report voluntarily mistakes done without fear of punishment, to raise concerns if something is seen to be not right without fear of repercussion and offering suggestions.¹ The reason being that some individuals may perceive that

engaging in the above mentioned behaviors, which is an integral part of effective team performance, may not be taken in good spirit by others and they may be considered as ignorant, incompetent, disruptive or negative thereby preventing them from engaging in these positive behaviors, as is evident in a psychologically safe work environment.^{2,3} It has been found in many studies that healthcare workers feel psychologically unsafe.⁴⁻⁸ Only 55% of staff feel comfortable speaking up, even if they notice a deficiency in patient care thereby decreasing the quality of patient care.⁵⁻⁷ This could be due to a professional hierarchy system evident in our profession. A study found that physicians felt significantly greater psychological safety than nurses, who in turn felt safer than respiratory therapists.⁸ In the multidisciplinary team, environment of intensive care for every member of the team is equally important. It is a global phenomenon that nonphysicians in the intensive care are usually apprehensive to voice their concerns, for fear of punitive measures as senior members of the team may be immune to such measures.⁹ In a study conducted among nurses almost half of them opined that their input is not well received.^{6,7} This has direct impact on patient outcome, as studies have shown that in units where staff feels psychologically unsafe more patients experience adverse events.⁹⁻¹¹ This is also substantiated by another study of clinical performance audit in which it was shown that in units where staff reported greater fear of repercussion on error reporting there is greater reduction of 12 key patient quality indicator.¹¹ Organizational and team research indicates professionals in psychologically unsafe teams are poor performers and are less likely to engage in behaviors that contribute to effective team.¹² First, they do not speak up concerns with suggestions, which are essential for a proper coordination of efforts; correct the errors and improvisation of processes.^{13,14} Nurses in psychologically unsafe units expressed less about medication errors. Second, individuals in psychologically unsafe teams engage less in team learning,¹ most importantly in health care, where teams are supposed to bring in new practices on a continuous basis. Many studies

have shown that units who had more learning activities had higher psychological safety, had successful implementation of new practices and lower patient mortality.¹⁵⁻¹⁷ Lastly, prediction of problem solving is more in psychologically safe environment, a major contributor to team success.^{18,19}

Enable the Development of Transactive Memory

Teams with experience often solve problems much better than new teams.²⁰ The term transactive memory is applied to the phenomenon where a team with experience perform better over a period of time, as their skills, knowledge and capabilities are retained in the memory of the team and utilized in a coordinated manner in future tasks.²¹ This enables the team members to be aware of each other's weaknesses and strengths, and like this group level memory facilitates multitasking like storage, retrieval and communication of information.²² Though the formal division of roles in the unit like, physician, nurses, etc. will remain, but within each group there may be unique skill shared by some team members. For example, one member of the team may be especially good in counseling the family members, while another is good in getting a vein. Having knowledge of these skills will help in deputing the correct person for that particular job. Moreover, this knowledge also helps all the team members to ask for help from appropriate person at the right time.²³⁻²⁵ When team members start recognizing that each once skills and expertise are deterrent but complementary (specialization). This is possible only when they trust in their teammates' expertise (credibility) coordination of task with work efficiency occurs as members develop high levels of specialization and credibility leading to high-team performance.

Essential attribute for transactive memory development is cognitive interdependence: individuals must recognize that their outcomes are dependent on the knowledge of others, and that others' outcomes are dependent on their knowledge.²⁶ Interdependence motivates for team members to recognize to what others contribute to the team.

There are many ways to instill cognitive interdependence in a team: through training and simulation, team-based rewards and development of positive work relationships. Informal interactions and shared experiences during daily rounds provide opportunities for members to learn about the relative expertise of other members, to coordinate who does what, to observe members' skills in action and to build positive relationships. Systems created by formal design (such as a listing of staff responsibilities or procedures in an ICU training manual) are validated and modified over a period of time as the team discovers the capability of members of team and their willingness to perform.²⁷ It takes time to develop a well-functioning transactive memory system.

Although studies of team transactive memory in organizations have focused on the benefits of member specialization building, a certain degree of overlapping

knowledge so that members can substitute for one another as necessary may be especially important for critical care teams, where team membership changes on a daily basis and nonroutine, time-sensitive, life-threatening decisions are commonplace.²⁸⁻³⁰

Team Leaders' Behavior Matters

Remember the difference between a boss and a leader; a boss says "Go" a leader says "let's Go".

EM Kelly

A well-documented contributor to team effectiveness is team leader's behavior.³¹ Lot depends on the role of team leader in the success of the team. A skilled leader would engage in structuring the team appropriately with right staff, define purpose of team members specifically and brief them about it, remove organizational barriers, and promote skills of individual member, and use their collective resources to fulfill team goals.³² Moreover, team leader is also a role model for other members of the team as the leader's behaviors is taken by the member as an indicator of what is expected from.³³ The term team climate is applied to the leadership behaviors and how it affects other members of the staff, which reflects on team capabilities. The team climate should be conducive to the psychological safety of the team members, in the sense that team leaders should seek and appreciates others input. They should also be available for counseling to other staff. An effective leadership contributes to positive psychological safety in the work environment and minimizes the differences between physicians and nonphysicians.⁸ This is also reflected in increased team learning and performance in these units.¹²

An effective leadership is reflected by a behavioral pattern of sharing power and giving more autonomy to subordinates, involve them in decision making, sharing knowledge, provide them with useful information, educating them, leading by example and showing genuine concerns for their doubts.^{34,35} This leads to higher level of team efficiency as has been shown in many team management studies from nonhealthcare organizations.³⁶ This also leads to increase in the job satisfaction of subordinates.¹⁵ It is important to note that many of these studies were conducted in management teams where teams were not making life and death decisions. Research on trauma resuscitation teams suggests that there may be other important contingencies for critical care teams.³⁷

An empowering leadership leads to improved feeling of psychological safety in the work environment, which will help the team members to speak up if they see a physician making an error during resuscitation.³⁸

CLINICIAN'S SYNTHESIS

There is little room for error in "high stake" environment of critical care and decisions need to be made promptly otherwise there is a possibility of immediate irreversible

end-organ dysfunction or death. Intra-team relationship is best exemplified during daily ward rounds and resuscitation scenarios. These activities, if analyzed, appropriately can lead to an insight on the effect of leadership, psychological safety and transactive memory in team effectiveness.

The relevant outcome measures for overall team performance can be considered using the input-process-output framework. Measurable inputs-influencing team performance includes: attributes of team members, including their knowledge, skills and attitudes relevant to teamwork and communication; the task at hand; environmental resources (e.g. availability of checklists and scheduled team briefings); and the organizational culture in which the team functions (e.g. valuing democracy in teams). Observable behaviors, as measured by teamwork measurement tools and compliance with established protocols and process measures. Output measures include: patient outcomes (complications, length of hospital stay and 30-day mortality); use of time and resources; and impact on staff (staff morale and staff retention) (Box 1).

During our critical care training we are not provided with any instructions on how to lead, organize and motivate teams. Consequently, we spend the first decade by trial and (frequent) error.

Change is "hard" even when implemented through gradual consensus-building, and there are easy ways and hard ways to achieve healthcare goals. Interdisciplinary rounds are the foundation of critical care. Stakes of the discussions and decisions are high, but there is ample time to build team skills and empowerment. During team meetings, a feature of strong leadership is let the others talk and refrain from taking a dominant position. This leads to increased psychological safety, which in turn promotes positive transactive memories. Though this may lead to longer ward rounds as viewpoints of participants will be taken, but this has appositive impact on patient care. This can be achieved by certain leadership practices during rounds. First, leaders should encourage active participation of others in a multidisciplinary (even when he thinks he knows the answer). Hierarchical structure usually inhibits nondoctors and junior team members from speaking up. A simple question like "have we missed anything?" may allow a bedside nurse to correct or add an

observation which might have been stated wrong earlier or was missed. This helps the psychological safety aspect not only of that nurse but other team members. This also helps transactive memory of the team members as they feel that their opinion is important to the team leader and they will be more keen to share their observation in future ward rounds. Teaching during ward rounds is another way of cultivating and promoting team spirit. Teaching must not be unilateral didacticism. All the members should be allowed to voice their ideas and meritorious suggestions should be implemented, thereby giving a positive impression to the team. Ward round should be a shared group learning experience. Another technique of effective positive team building is to regularly name team victories and failures. The failures need to be discussed in a nonaccusatory debriefing style. It is even more important for the team leader to accept his failure, if any, which acknowledges fallibility, thereby giving positive signals to others. This helps in self-reporting of errors in the system. Similarly, team victories can be named and shared. Just like in sport a positive outcome is not only one person's contribution, but collective effort of every team member. Monthly quality assurance (QA) meetings are an excellent opportunity to build up on team science. Each QA member can bring forward their concern, which can be discussed among members and a solution addressed and implemented and reaudited.

CASE VIGNETTE

A young man with variceal hemorrhage had a variceal banding shortly after admission, but soon he had a massive hematemesis. In the ensuing 2 hours, he was attended by three nurses, a respiratory therapist, gastroenterologist, three residents, one fellow, sometimes simultaneously. Multiple interventions were done by different team members at different times and in quick succession. The team members shared their activities and after multiple bloods and other blood product transfusion and procedures he was stable and not one organ system had failed. Each member's individual training and excellence, coupled with our team's transactive memory and psychological safety (opinions that differed from the leader), resulted in an optimal outcome. This coordinated effort of team members was only possible due to transactive memory from daily rounds and previous resuscitations, as the team members knew what to do, they were comfortable acting independently, they did not wait for orders from above and were ready to speak out their opinion. "Contingent leadership" that is determined by the venue or situation becomes more directive than during rounds.

CONCLUSION

Based on findings from the most recent research evidence in medicine and management, four principles are identified for improving the effectiveness of team working in intensive

Box 1: Input-process-output framework for measuring team performance

Input	Output
<ul style="list-style-type: none"> Individual attributes Team composition The task Environmental resources Organizational culture Process Teamwork behavior Compliance with protocols 	<ul style="list-style-type: none"> Patient outcomes Resource utilization Staff satisfaction

care; engender professional efficacy, create stable teams and leaders, develop trust and participative safety and enable frequent team reflexivity.³⁹⁻⁴¹

In spite of sound logic, the data are still not out there to establish a cause and effect relationship between application of behavioral sciences and improvement of ICU outcome. The mainstay of ICU management is team building and this skill needs to be promoted through educational initiatives. This might include formal training in behavioral sciences to young clinicians as a complimentary skill in addition to their core medical skills. It is the critical team, which delivers the whole care and it is intuitive that patient outcome will depend on the entire teams performance more than brilliance of any one individual team member. It is imperative that these skills are part of early training curriculum rather than learning by trial and error over a period of time with detrimental effects on patient outcome.

REFERENCES

- Edmondson AC. Psychological safety and learning behaviour in work teams. *Administrative Sci Quart.* 1999;44:350-83.
- Edmondson AC. Managing the risk of learning: Psychological safety in work teams. In: West M, Tjosvold D, Smith KG (Eds). *International Handbook of Organizational Teamwork and Cooperative Working*. London: John Wiley & Sons; 2003. Pp. 255-76.
- Kahn WA. Psychological conditions of personal engagement and disengagement at work. *Acad Management J.* 1990;33:692-724.
- Edmondson AC. Learning from mistakes is easier said than done: Group and organizational influences on the detection and correction of human error. *J Appl Behavioral Sci.* 2004;32:5.
- Thomas E, Sexton J, Helmreich R. Discrepant attitudes about teamwork among critical care nurses and physicians. *Crit Care Med.* 2003;31:956-9.
- Sexton JB, Makary MA, Tersigni AR. Teamwork in the operating room: Frontline perspectives among hospitals and operating room personnel. *Anesthesiology.* 2006;105:877-84.
- Sexton JB, Holzmuller CG, Pronovost PJ. Variation in caregiver perceptions of teamwork climate in labor and delivery units. *J Perinatol.* 2006;26:463-70.
- Nembhard IM, Edmondson AC. Making it safe: The effects of leader inclusiveness and professional status on psychological safety and improvement efforts in health care teams. *J Organizational Behavior.* 2006;27:941-66.
- Maxfield D, Grenny J, McMillan R. *Silence Kills: The Seven Crucial Conversations for Healthcare*. Provo, UT: VitalSmarts, LC; 2005.
- Rathert C, Ishqadeif G, May DR. Improving work environments in health care: Test of a theoretical framework. *Health Care Management Rev.* 2009;34:334-43.
- Singer S, Lin S. Relationship of safety climate and safety performance in hospitals. *Health Services Res.* 2009;44:399-421.
- Nembhard IM, Edmondson AC. Psychological safety: A foundation for speaking up, collaboration and experimentation. In: Cameron K, Spreitzer G (Eds). *The Oxford Handbook of Positive Organizational Scholarship*. Oxford: Oxford University Press; In press.
- Detert JR, Burris ER. Leadership behavior and employee voice: Is the door really open? *Acad Management J.* 2007;50:869-84.
- Siemsen E, Roth AV. The influence of psychological safety and confidence in knowledge on employee knowledge sharing. *Manufacturing Service Operations Management.* 2009;11:429-47.
- Siemsen E, Roth AV, Balasubramanian. The influence of psychological safety and confidence in knowledge on employee knowledge sharing. *Manufacturing Service Operations Management.* 2009;11:429-47.
- Tucker AL, Nembhard IM, Edmondson AC. Implementing new practices: An empirical study of organizational learning in hospital intensive care units. *Management Sci.* 2007;53:894-907.
- Nembhard IM, Tucker AL. Deliberate learning to improve performance in dynamic service settings: Evidence from hospital intensive care units. *Organization Sci.* 2010;22:1-16.
- Tucker AL. An empirical study of system improvement by frontline employees in hospital units. *Manufacturing Service Operations Management.* 2007;9:492-505.
- Halbesleben JRB, Rathert C. The role of continuous quality improvement and psychological safety in predicting work-arounds. *Health Care Management Rev.* 2008;33:134-44.
- Hollingshead AB, Gupta N, Yoon K, et al. Transactive memory theory and teams: past, present, and future. In: Salas E, Fiore SM, Letsky M (Eds). *Theories of Team Cognition: Crossdisciplinary Perspectives*. New York: Taylor & Francis; 2011. Pp. 421-455.
- Moreland RL. Transactive memory: Learning who knows what in work groups and organizations. In: Thompson L, Messick D, Levine J (Eds). *Sharing Knowledge in Organizations*. Hillsdale, NJ: Lawrence Erlbaum; 1999. Pp. 3-31.
- Hollingshead AB. Transactive memory. In: Levine J, Hogg M (Eds). *Encyclopedia of Group Processes and Intergroup Relations*. Thousand Oaks, CA: Sage; 2009. pp. 931-3.
- Wegner DM. A computer network model of human transactive memory. *Social Cognition.* 1995;13:319-39.
- Hollingshead AB, Brandon DP. Potential benefits of communication in transactive memory systems. *Hum Commun Res.* 2003;29:607-15.
- Lewis K. Measuring transactive memory systems in the field: Scale development and validation. *J Appl Psychol.* 2003;88:587-604.
- Hollingshead AB. Cognitive interdependence and convergent expectations in transactive memory. *J Personality Social Psychol.* 2001;81:1080-9.
- Brandon DP, Hollingshead AB. Transactive memory systems in organizations: Matching tasks, expertise, and people. *Organization Sci.* 2003;15:633-44.
- Tschan F, Semmer NK. Explicit reasoning, confirmation bias, and illusory transactive memory: A simulation study of group medical decision making. *Small Group Res.* 2009;40:271-300.
- Hunziker S, Tschan F. Hands-on time during cardiopulmonary resuscitation is affected by the process of teambuilding: a prospective randomized simulator-based trial. *BMC Emerg Med.* 2009;9:3.
- Michinov E, Olivier-Chiron E, Rusch E, Chiron B. Influence of transactive memory on perceived performance, job satisfaction and identification in anaesthesia team. *Br J Anaesth.* 2008;100:327-32.
- Hogan R, Curphy GJ, Hogan J. What we know about leadership. *Am Psychol.* 1994;49:493-504.
- Hackman JR, Wageman R. A theory on team coaching. *Acad Management Rev.* 2005;30:269-87.
- Tyler TR, Lind EA. A relational model of authority in groups. *Adv Exp Psychol.* 1992;25:115-91.
- Srivastava A, Bartol KM, Locke EA. Empowering leadership in management teams: effects on knowledge sharing, efficacy, and performance. *Acad Management J.* 2006;49:1239-51.
- Arnold JA, Arad S, Rhoades JA, et al. The empowering leadership questionnaire: The construction and validation of a new scale for measuring leader behaviors. *J Organizational Behavior.* 2000;21:249-69.
- Morrison R, Jones L, Fuller B. The relation between leadership style and empowerment on job satisfaction of nurses. *J Nursing Admin.* 1997;27:27-34.
- Yun S, Faraj S, Xiao Y, et al. Team leadership and coordination in trauma resuscitation. In: Beyerlein M (Ed.). *Advances in Interdisciplinary Studies of Work Teams, Volume 9*. Bingley, UK: Emerald Group Publishing Limited; 2003:189-214.
- Gupta N, Hollingshead AB. Differentiated versus integrative transactive memory effectiveness: It depends on the task. *Group Dynamics.* 2010;14:384-98.
- Manthous CA, Amoateng-Adjepong Y, et al. Effects of a medical intensivist on patient care in a community teaching hospital. *Mayo Clin Proc.* 1997;72:391-9.
- Shortell SM, Zimmerman JE. The performance of intensive care units: Does good management make a difference? *Med Care.* 1994;32:508-25.
- Manthous CA, Hollingshead AB. Team science and critical care. *Am J Respir Crit Care Med.* 2011;184:17-25.

"Big Data" in Critical Care: Current Status

Subhash Todi

INTRODUCTION

The foundation of intensive care unit (ICU) is based on close monitoring of organ function, which is usually done continuously by invasive and noninvasive means. Moreover, in the modern investigation-oriented ICUs, further data are gathered from the support departments like radiology, biochemistry, and microbiology. This leads to generation of enormous database for individual patient. With the increasing use of Electronic Medical Record (EMR), which has become almost mandatory in the ICUs of developed countries and advent of electronic ICUs, data archiving has become increasingly easy. With these advances come the issue of information overload, and a possibility of inappropriate use of these data. This chapter will discuss the ways by which the big data in ICU can be used in a meaningful way.^{1,2}

APPLICATION

The requirement of critical care beds are going up worldwide constituting almost 10% of all hospital beds.³ Intensive care units have a unique opportunity of collecting, archiving, and analyzing data and use it in a meaningful way in an ongoing learning environment. Evidence is lacking or equivocal in many critical care decisions and information gathered from the observational data are becoming important in making empirical decisions. In this paradigm, a universal deidentified patient database archived in electronic cloud is queried with the clinical data of a particular patient, and intervention planned, and outcome of similar patient with this intervention is retrieved and integrated into patients electronic medical record as a clinical decision support system.⁴

Pharmacovigilance is another way by which this information superhighway may become useful. Adverse effects, drug interactions and dosing, etc. of a particular drug on an individual patient may be compared to population database of similar patient.

One of the important use of big data is the use in various scoring system like Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Mortality Prediction Model (MPM) for prognostication of critically ill and this is arrived at by analyzing a large number of data in a derivation cohort and statistically analyzing the prognostic variables and validating it in another cohort. These scoring systems are used for calculating predicted mortality and when compared to observed mortality gives a standardized mortality ratio (SMR), which is an indicator of quality control and comparative performance of ICUs. This is one example of direct application of big data from an administrative angle.⁵

CURRENT STATUS

Many commercial vendors of electronic health records have initiated process of gathering millions of data bits and partnering with academia for research and administrative purposes. Moreover, these data are collected real time and improve point of care decision taken by the clinician. This process is already been used extensively in business world and is termed business intelligence, and it has been found to improve the operational efficiency, quality, and a competitive advantage. Healthcare need to adopt a similar industry model, which may be termed as clinical intelligence, to achieve a goal of providing optimum patient care. Philips electronic ICU database adds almost 400,000 patient data every year to its database and makes it available commercially.⁶ On the other hand, Multiparameter Intelligent Monitoring in Intensive Care (MIMIC II) is a public access database, which contains detailed deidentified patient data including International Classification of Disease discharge diagnosis, hemodynamics and ventilatory variables, nursing input data, drug data, and can be accessed online for a comparative performance evaluation by any ICU.⁷ Analysis of this database has resulted in many pertinent observations like outcome of troponin-positive patients, heterogeneous

effect of red blood cell transfusion in various populations, and optimization of heparin dosing. These observations may be applicable specifically to the hospital from which it was generated and need to be compared with other database for generalizability. With increasing use of smartphones, various applications have been devised, which can store patients vital signs and transmit their electrocardiographic signals. A genomic data bank is another offshoot of big data and is a major step toward individualized and precision medicine movement. This has already come in the clinical arena in oncology and pharmacotherapy and hopefully will enter into critical care practice. This will help us to individualize patient treatment and tailor their drug therapy based on genetic markers.

In order to popularize the concept of big data and developing consensus on its optimal use, crowd sourcing and data marathon and hackathon may be planned, which will bring unlimited number of practitioners together, similar to Facebook and Twitter, where they can share their experiences. In a recently conducted data marathon, healthcare practitioners including physicians, nurses, pharmacists, and other paramedical staff along with information technology experts, computer scientist, data scientist, and epidemiologist interacted to answer many critical care-related questions by using big data, like utility of using paracetamol for fever control in ICU, optimum blood pressure level in septic shock patients, as literature is equivocal on these problems. The consensus, which came out from this brain-storming meeting was that open data access, which is systematically collected and shared transparently and utilized meaningfully is the way forward from the current era of working in silos and not utilizing optimally the digital revolution taking place around us.⁸ In order for this explosion of data mining to be useful a close collaboration of clinician and nonclinical support systems like statistician, will be needed, where the clinical data can be analyzed meaningfully given the innumerable variables that is inbuilt in such kind of data collection system. The "noise" from these data bank will need to be teased out and a clinically applicable and user friendly format need to be presented.

USE IN CLINICAL RESEARCH

Randomized-controlled trial (RCT) does not answer many of the day-to-day clinical questions that arise while managing these patients. Even if an RCT is available, because of the trial exclusion criteria, many results are not applicable to a considerable number of patients. Dynamic clinical data mining report on the other hand presents dynamic observational data of intervention and outcome in similar group of patient and helps in making more informed decision.^{9,10}

From a research perspective a retrospective observational study can be conducted on these databases and through appropriate statistical adjustments like propensity matching

and other quasi randomization model, conclusion may be derived which will establish close association if not causality between different variables. One of the limitations of using EMR data for research purpose is that it was not constructed for this purpose, and have various design structures, layouts, and organized differently, making comparison of data difficult. Moreover, they are highly dependent on expertise of data entry operator and can have artifacts, errors, and missing values. Recently, there is an increasing movement by academic institutions and industry to make their big research data universally and publicly accessible, thereby allowing other researchers to generate new hypothesis and further progress based on this database. One such open access clinical data bank is Yale University Open Data Access. Many of this data will be from critical care research, thus advancing this field tremendously.^{11,12}

From an individual hospital perspective, the big data can be archived and analyzed by data managers with certain specific goals in mind, e.g., collecting data for insured versus noninsured patient and their cost of care and outcome. This may help in proper resource allocation, budgeting, and policy decision in that particular hospital, thus giving credence to investing in this technology.

BARRIERS

Obstacles to adoption of this technology in healthcare sector have been the relatively late adoption of electronic medical records by the healthcare practitioners, initial investment cost, fear about the loss of patient confidentiality, poor integration between different information system technology within the healthcare, poor training of healthcare staff, etc. Patient privacy has been considered as one of the major barriers of data-driven learning system as there is a risk of reidentification, litigation issues. Moreover, patients are reluctant to give consent to share data with the perceived notion of it being used for marketing by pharmaceutical industry and for quality improvement measures, which will benefit corporate hospital. This will require more public education to disseminate the information about the importance of data sharing. A close collaboration will be needed between government, industry, and healthcare institution to protect the intellectual property rights as addressed by United States critical illness and injury trial group. As the electronic data in majority of cases are still entered manually with its inherent problems, automated data entry directly from the monitor and other support structure like laboratory and imaging will reduce the errors and improve the quality of data. A panel of critical care expert has opined that lack of condensation of this data for a meaningful application at the bedside as one of the major barrier for acceptance of this technology by the physicians. It was suggested by this panel that basics of big data applicability should be included in the medical curriculum for students and trainees and inclusion of clinician or other end users at

the design stage will make this technology customer friendly and more easily acceptable.

LIMITATION

One of the limitations of big data is erroneous conclusions that may be derived called "big data hubris" as exemplified by overestimation of flu epidemic by flawed data tracking of number of patients with flu initiated by Google.^{13,14} Biased collection of data will make validation and generalization difficult, but due to sheer large-sample size, this bias, which is inherent in any data collection and will be less evident and chances of false-positive results which are clinically unsafe, will be less in big data-based research methodology as opposed to randomized studies and small observational trials, as is evident by contradictory results of these trials by various researchers depending upon the risk adjustment.

CONCLUSION

In the growing digitalized world around us, healthcare industry need to keep pace with this by adopting the electronic medical record, automated data entry from various clinical and laboratory portals, and archiving this data in a definite searchable format. The utility of this big database, if carefully analyzed, will help not only in clinical research but also in clinical management. This is the most important step toward delivering precision medicine in critical care.

REFERENCES

1. Ghassemi M, Celi LA, Stone DJ. State of the art review: the data revolution in critical care. *Crit Care*. 2015;19:118.
2. Celi LA, Csete M, Stone D. Optimal data systems: the future of clinical predictions and decision support. *Curr Opin Crit Care*. 2014;20:573-80.
3. Vincent JL. Critical care—where have we been and where are we going? *Crit Care*. 2013;17:S2.
4. Celi LA, Mark RG, Stone DJ, Montgomery RA. "Big data" in the intensive care unit. Closing the data loop. *Am J Respir Crit Care Med*. 2013;187:1157-60.
5. Breslow MJ, Badawi O. Severity scoring in the critically ill: part 1—interpretation and accuracy of outcome prediction scoring systems. *Chest*. 2012;141:245-52.
6. McShea M, Holl R, Badawi O. The eICU research institute—a collaboration between industry, health-care providers, and academia. *IEEE Eng Med Biol Mag*. 2010;29:18-25.
7. Lee J, Scott DJ, Villarreal M, et al. Open-access MIMIC-II database for intensive care research. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:8315-8.
8. Badawi O, Brennan T, Celi LA, et al. Making big data useful for health care: a summary of the inaugural mit critical data conference. *JMIR Med Inform*. 2014;2:e6.
9. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914.
10. Celi LA, Zimolzak AJ, Stone DJ. Dynamic clinical data mining: search engine-based decision support. *JMIR Med Inform*. 2014;2(1):e13.
11. Celi LA, Moseley E, Moses C, et al. From pharmacovigilance to clinical care optimization. *Big Data*. 2014;2:134-41.
12. Krumholz HM, Ross JS, Gross CP, et al. A historic moment for open science: the Yale University Open Data Access project and Medtronic. *Ann Intern Med*. 2013;158:910-1.
13. Lazer D, Kennedy R, King G. Big data. The parable of Google Flu: traps in big data analysis. *Science*. 2014;343:1203-5.
14. Butler D. When Google got flu wrong. *Nature*. 2013;494:155-6.

Section 9

Pediatrics

SECTION EDITOR: BANANI PODDAR

What Really Makes the Difference to Outcomes in Pediatric Sepsis?

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INTRODUCTION

What is Sepsis?

Sepsis is defined as systemic inflammatory response syndrome (SIRS) in the presence of or as a result of a suspected or proven infection. Systemic inflammatory response syndrome is defined as the presence of two of the four criteria, one of which must include either an abnormal temperature or abnormal white cell count. Severe sepsis

or septic shock is defined as the presence of sepsis and features of end-organ dysfunction (Box 1). However, in its broadest sense, most children who die from an infection have succumbed to sepsis as the final common pathway.

The International Pediatric Sepsis Consensus Conference modified the adult SIRS criteria for children, and revised the definitions for pediatric septic shock and severe sepsis.¹ They also outlined age-specific vital signs and laboratory data (Table 1).

Box 1: Criteria for systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock

Systemic inflammatory response syndrome (SIRS)

- The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:
 - Core temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimuli, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over 0.5–4 h time period OR for children <1 year old: bradycardia, defined, as a mean heart rate $<10^{\text{th}}$ percentile for age in the absence of external vagal stimulus, β -blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5 h time period
 - Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
 - Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or $>10\%$ immature neutrophils

Infection

- A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

- SIRS in the presence of or as a result of suspected or proven infection

Severe sepsis

- Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress OR two or more organ dysfunctions

Septic shock

- Sepsis and cardiovascular organ dysfunction

TABLE 1 Age-appropriate heart rate, respiratory rate, leukocyte count, and systolic blood pressure

Age group	Heart rate (beats/min)		RR (breaths/min)	WBC count (leukocytes $\times 10^3$ /mm)	SBP (mmHg)
	Tachycardia	Bradycardia			
0 days–1 week	>180	<100	>50	>50	<65
1 week–1 month	>180	<100	>40	>19.5 or <5	<75
1 month–1 year	>180	<90	>34	>17.5 or <5	<100
2–5 years	>140	NA	>22	>15.5 or <6	<94
6–12 years	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 years	>110	NA	>14	>11 or <4.5	<117

RR, respiratory rate; WBC, white blood cell; SBP, systolic blood pressure.

INCIDENCE AND OUTCOMES

Sepsis accounts for a significant number of admissions to pediatric intensive care units (PICU) and about 60% of the 6 million of deaths in neonates and under 5 years worldwide; deaths which are usually attributable to pneumonia, diarrhea, malaria, and any invasive infection.²⁻⁴ The hallmark of all these pathogenic infections is multiple organ dysfunction leading to severe sepsis and septic shock and catastrophic outcomes. Estimates in children are hard to come by, but recent data from the developed world shows rising incidence and mortality, which is lower than before, but still high. In the United States, a study of 43 children's hospitals from 2004 to 2012 showed an increasing point prevalence of pediatric severe sepsis (PSS) from 6.2–7.7% with an increase in comorbidities, a decrease in the mortality rate from 18.9 to 12%, and a tremendous burden on resources. An increased incidence of PSS and a significant decrease in mortality rate were also reported among critically ill children in Australia and New Zealand⁵ as there were declines in both hospitalization and mortality rate, but still has a significant burden on the national health resources in Canada.⁶ Moreover, sepsis from hospital-acquired multidrug-resistant Gram-negative organism is associated with higher incidence and higher mortality rate in European PICUs.⁷

Data for sepsis in children from low- and middle-income countries is lacking and is bundled into deaths from the major killers, which are pneumonia, malaria, and diarrheal diseases. However, sepsis is usually the final common pathway to death from infections, and thus, sepsis-related pediatric deaths in low- and middle-income countries is grossly underestimated.² While data from the developed countries show increasing prevalence with decreasing mortality in pediatric sepsis due to early intervention and use of guideline, limited data from low- and middle-income countries still show consistently high incidence and high mortality rates.^{8,9}

A global, but mostly developed countries point prevalence study (SPROUT study) of PSS in PICUs reported that sepsis contributes to more than 8% of all critically ill children and 25% of hospital mortality with 25% showing

signs of new functional disability and 33% progressive organ dysfunction.¹⁰ That prevalence and outcomes vary widely can be partly attributable to the absence of a universally accepted definition, lack of a gold standard diagnostic test, and varying diagnostic capabilities, to diagnose sepsis. Thus, approaches to diagnosis among clinicians vary and it is, therefore, not surprising that public awareness about this major public health burden is lacking which dampens incentives for policy makers to act. Indeed, lack of awareness is universal as evidenced by an international survey, which showed that most people have not heard about the word sepsis; and about two-third of the doctors surveyed were concerned about the lack of a common definition.¹¹

COMPREHENSIVE APPROACH TO SEPSIS MANAGEMENT

Decreasing the burden and improving outcomes in pediatric sepsis can be best achieved by considering sepsis as a major public health threat. This paradigm would lend itself to a multifaceted management approach based on the concept of prevention. Prevention using the public health paradigm by a comprehensive approach; combining primary, secondary, and tertiary prevention ensures the best chance of success (Fig. 1).

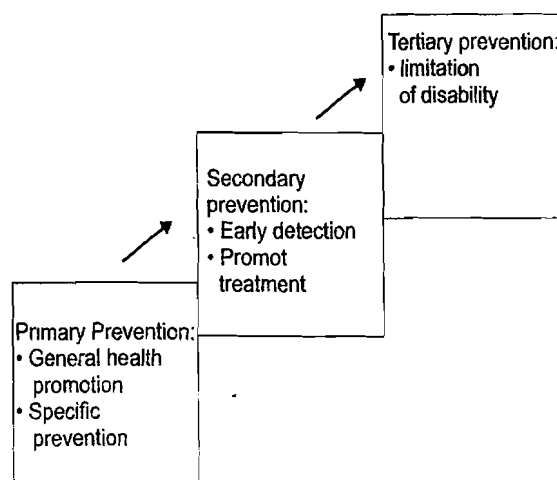


FIG. 1: Levels of prevention in pediatric sepsis

Management and Outcomes of Pediatric Sepsis

Diagnosis

The SIRS criteria were crafted by consensus opinion and have not been subjected to validation, and there is no data to support the requirement of two SIRS criteria for complete definition of severe sepsis.¹² However, it is used extensively as screening tool in febrile ill looking children for sepsis workup and prompt treatment. While the SIRS-based definition of sepsis has very high sensitivity in identifying children who died during hospitalization in a Ugandan hospital, it has very low specificity.¹³ In addition to the age-specific vital signs and laboratory data, some biomarkers could be used to supplement clinical assessment and aid in the early diagnosis and monitoring of treatment of sepsis syndrome in children in such settings.¹⁴ They are by themselves not confirmatory and there is no standardized practice for their use. C-reactive proteins (CRP) are elevated in both inflammatory and infectious conditions while procalcitonin has been shown to differentiate infections from inflammation. Other candidate biomarkers include interleukin-18 and CD64. Serum lactate level is useful both in distinguishing septic shock from sepsis, and in the monitoring of treatment of septic shock. Proteomics are still preliminary, but they offer great benefits in elucidating the pathophysiology of sepsis, and provide vital opportunity for diagnosis, management, and prognostication of sepsis.¹⁵

The approach to sepsis diagnosis is context dependent, and sepsis definitions above were developed for sepsis identification and goal-directed therapy in clinical settings in the developed countries and may limit sepsis identification in low- and middle-income countries.¹⁶ Wiens et al. suggested that the more pragmatic alternative for sepsis definition and identification would be to exclude the laboratory (leukocyte) requirement for SIRS definition since some centers in resource-limited countries might not have the resources to obtain these laboratory data. A modified definition of sepsis would be based solely on clinical findings of heart rate, respiratory rate, and core temperature (with abnormal temperature being a requirement). In a study in Latvia, SIRS was commonly identified by a combination of fever and respiratory rate more than two standard deviations above normal for age.¹⁷ In resource-limited settings, sepsis diagnosis should be context and resource availability driven, and in low- and middle-income countries with the highest burden and least resources should de-emphasize the need for laboratory-based diagnosis. Along these lines, the presence of abnormal temperature together with abnormal respiratory rate or abnormal heart rate or change in skin or mucous membrane color or change in mental status should trigger sepsis management. A study in

Bangladesh, a model using oxygen saturation, respiratory rate, and temperature abnormalities in addition to other physical findings predicted the need for hospital admission in children (mostly from infections) with a sensitivity of 77% and specificity of 87%.¹⁸

What Makes the Difference to Outcomes in Pediatric Sepsis?

Improved outcomes rest on a systematic and comprehensive approach that would incorporate primary prevention to ensure that children live healthy lifestyle. When sepsis intervenes, early recognition and prompt treatment (secondary prevention) ensures optimal outcomes. Upon discharge from the hospital, proper rehabilitation (tertiary prevention) and adequate follow-up should be arranged to ensure decreased morbidity and mortality.

Primary Prevention: General Health Promotion and Specific Prevention

Every effort to reduce global morbidity and mortality from sepsis must include the use of preventive strategies.¹⁹ These will include measures to prevent the occurrence of sepsis such as good hand hygiene, provision of clean portable water, adequate nutrition, immunization, antibiotic prophylaxis, zinc supplement, and priority public policy to promote awareness and research in the field of sepsis.

Immunization

The global burden of sepsis can be reduced by improved vaccinations.²⁰ Heterologous immunization with *Bacillus* *C*amille-Guerin (BCG) vaccine showed a lower mortality rate among BCG-vaccinated children than BCG-unvaccinated low birth weight children, and this probable beneficial effect could not be explained by protection from tuberculosis alone.^{20,21} Likewise, specific vaccines reduce mortality and morbidity from the specific infectious diseases like *Haemophilus influenzae* type B (HIB), Meningococcal meningitis, measles, etc.

Antibiotics Prophylaxis

Antibiotics prophylaxis, though fraught with concerns for emergence of resistance, plays a vital role in preventing severe sepsis from specific groups of patients. Prophylaxis reduces the risk of invasive diseases from Group B *Streptococcus* in neonates; encapsulated organisms in patients with asplenia; and from subacute bacterial endocarditis in patients with structural heart defects.¹⁹ Application of appropriate antibiotic prophylaxis in established disease conditions may decrease mortality and reduce disabilities associated with some severe bacterial infections.

Hand Hygiene

Hand washing has been known to reduce fecal-oral transmission of organisms that cause acute gastroenteritis in the developing worlds, and hospital-acquired infections worldwide. Lam et al. found that healthcare-associated infection rate decreased from 11.3 to 6.2 per 1,000 patient days with improved overall hand hygiene compliance.²²

Nutrition

Nutrition plays a big role in both sepsis prevention and early management of sepsis in children.²³ About 50% of children in low- and middle-income countries with sepsis are malnourished, and this complicates management and leads to poorer outcomes. Severely malnourished under-five children with severe sepsis and pneumonia, who require fluid resuscitation in addition to antibiotics, show higher case fatality rate when compared to those without severe sepsis.²⁴

Secondary Prevention: Early Diagnosis (Recognition) and Treatment

Early detection of sepsis and early aggressive therapy can improve outcomes in sepsis. Early recognition and prompt goal-directed therapy should start from the point of first contact with the patient. This could be by community health workers, the paramedic ambulance personnel, physicians at district and community hospitals, emergency departments (EDs), and PICU. With sepsis resolution, postdischarge follow up, especially for the identified vulnerable population, should be ensured.

Prehospital/Preintensive Care Unit Sepsis Interventions

Education of the lay public and paramedics and community health workers to recognize sepsis in the field, and initiate treatment en-route the hospital for definitive therapy is essential.

In resource-limited settings, community health workers, community health volunteers, or any organized and trained primordial level health personnel could identify possible severe bacterial infections from newborns to childhood, and administer the first dose of antibiotics prior to transfer of the sick newborn/child to the next level of care. In Nepal, a community-based pilot program called Morang Innovative Neonatal Intervention (MINI) program was successful in getting female community health volunteers (FCHVs) to visit homes of newborn babies to identify those who have possible severe bacterial infection, give them first dose of cotrimoxazole, and then refer to the facility-based community healthcare workers (CHWs) for further 7-day gentamicin

treatment.²⁵ In this study, they found that assessment of signs by the FCHVs matched those by the more highly trained CHW in over 90% of the cases. The case fatality rate among those who received the complete gentamicin treatment was 1.5% compared to 5.3% among those who did not initiate the treatment.

Management of Pediatric Severe Sepsis in the Emergency Department

In the ED, outcome is influenced by prompt recognition of sepsis and septic shock, activation of septic bundle, and goal-directed therapy in the first hour. The 2014 guideline emphasizes:

- First hour fluid resuscitation and inotropic agents directed at goals of threshold heart rates, normal blood pressure, and capillary refill less than or equal to 2 seconds with specific evaluation after each bolus for signs of fluid overload as well as first hour antibiotic administration.

To maintain consistency and structure toward achieving goal-directed therapy, the 2014 guideline identified three management bundles namely; (i) recognition bundles, (ii) resuscitation and stabilization bundles, and (iii) performance bundles. The details of these of management bundles in the emergency management of PSS are as follows.

Recognition Bundle

It contains triggers that will enhance rapid identification of suspected sepsis in the institution. This bundle has three components:

1. Trigger tool: This includes vital signs, physical examination, and risk factors. Any positive trigger should prompt rapid physician assessment and or initiation of sepsis protocol. See trigger tools in figure 2
2. Rapid clinician assessment: Any patient identified as having suspected sepsis based on the triggers tools should be assessed by a clinician within 15 minutes
3. Activation of the sepsis bundle: Sepsis bundle should be activated within 15 minutes of clinician assessment of a patient suspected of having sepsis.

Resuscitation and Stabilization Bundle

This ensures rapid treatment, and has five action items:

1. Place intraosseous or intravenous access within 5 minutes
2. Start appropriate fluid resuscitation within 30 minutes
3. Initiate broad spectrum antibiotics within 60 minutes
4. Send blood culture, if it does not delay antibiotics administration
5. Start peripheral or central inotropes based on response to fluid infusion (Figs 3 and 4).

Pediatric septic shock collaborative septic shock identification tool

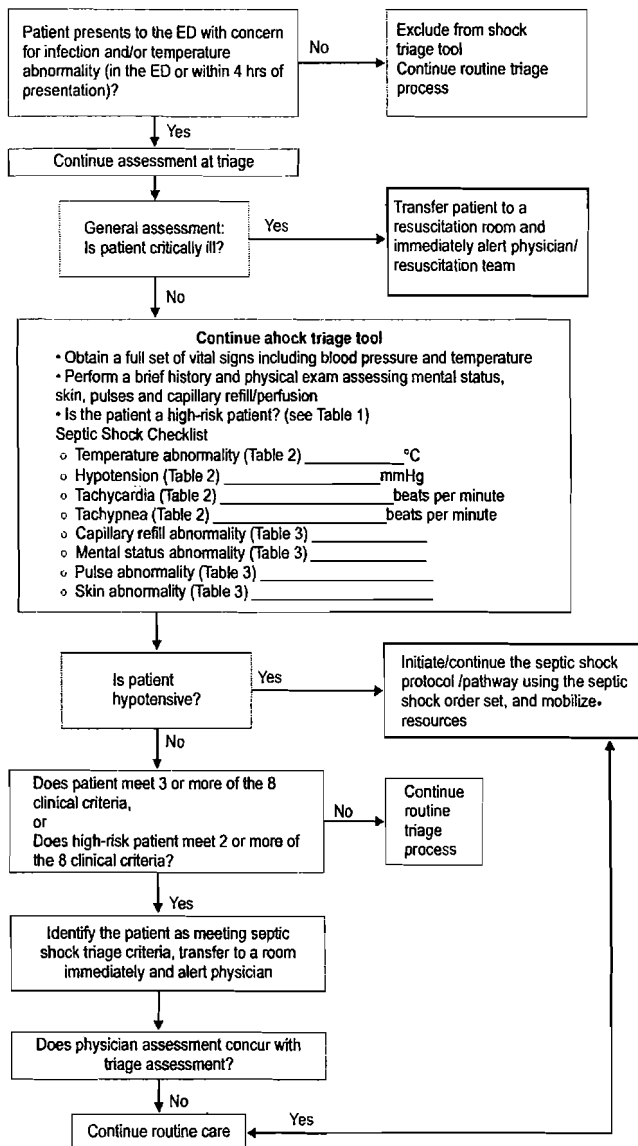


FIG. 2: Trigger tools for rapid pediatric sepsis identification

Ongoing management of severe sepsis in the pediatric intensive care unit

To improve outcome, subsequent ICU stabilization goals of central venous oxygen saturation (SvO₂) more than 70% and cardiac index of 3.3–6.0 L/min/m² should be maintained. This includes continuing with peripheral concentration of inotrope started in the ED until a central venous line is established.²⁶ The details of the stabilization bundles might include two additional items namely:

1. Multimodal monitoring to attain and maintain goal therapies at normal mean arterial pressure-central venous pressure (MAP-CVP) ($55 + 1.5 \times \text{age in years}$), and ScvO₂ more than 70% and/or cardiac index 3.3–6.0 L/min/m²
2. Appropriate antibiotics treatment with identification and source control.

Table 1. High Risk Conditions

- Malignancy
- Asplenia (including SCD)
- Bone marrow transplant
- Central or indwelling line/catheter
- Solid organ transplant
- Severe MR/CP
- Immunodeficiency, immunocompromise or immunosuppression

Table 2. Vital Signs (PALS)

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0 d – 1 m	> 205	> 60	< 60	<36 or >38
≥ 1 m – 3 m	> 205	> 60	< 70	<36 or >38
≥ 3 m – 1 y	> 190	> 60	< 70	<36 or >38.5
≥ 1 y – 2 y	> 190	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 2 y – 4 y	> 140	> 40	< 70 + (age in yr × 2)	<36 or >38.5
≥ 4 y – 6 y	> 140	> 34	< 70 + (age in yr × 2)	<36 or >38.5
≥ 6 y – 10 y	> 140	> 30	< 70 + (age in yr × 2)	<36 or >38.5
≥ 10 y – 13 y	> 100	> 30	< 90	<36 or >38.5
> 13 y	> 100	> 16	< 90	<36 or >38.5

Table 3. Exam Abnormalities

	Cold Shock	Warm Shock	Non-specific
Pulses (central vs. peripheral)	Decreased or weak	Bounding	
Capillary refill (central vs. peripheral)	≥ 3 sec	Flash (< 1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental status			Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

If shock is not reversed with appropriate fluids and inotropic agents, and patient is deemed catecholamine-resistant shock, hydrocortisone should be started, if there is any risk of absolute adrenal insufficiency (Fig. 3). In persistent catecholamine-resistant shock after you have ruled out any intrathoracic obstructive pathology, and shock is not reversed, extracorporeal membrane oxygenation (ECMO) may be considered.

Extracorporeal therapies

The use of ECMO in PSS has been associated with decreased mortality and significantly increased survival among patients with severe sepsis and malignant comorbidities who were on ECMO and renal replacement therapies.²⁷ Similarly, McLaren et al. demonstrated that central ECMO has even

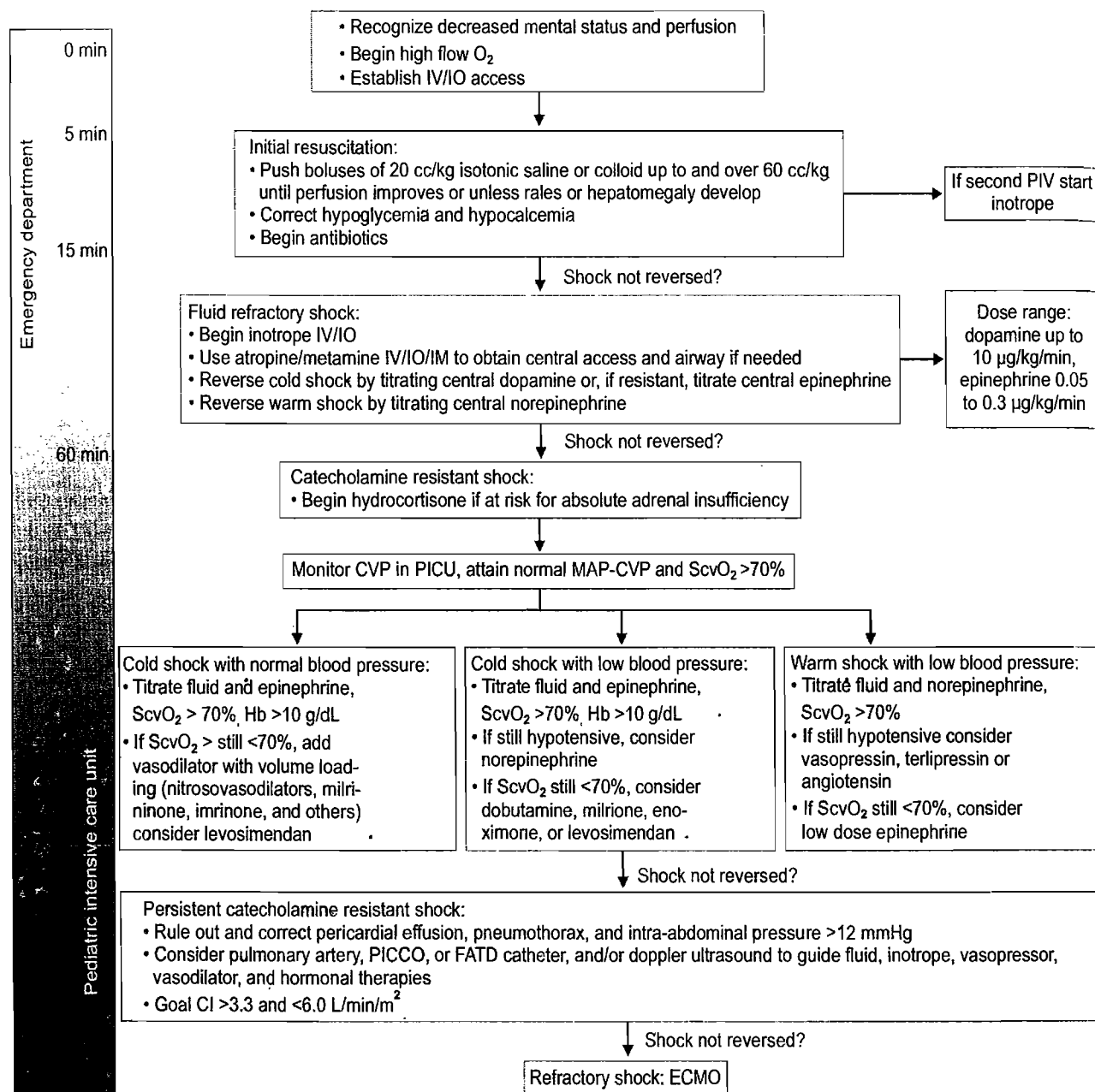


FIG. 3: Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in infants and children

better outcome than peripheral ECMO in refractory pediatric septic shock.²⁸ The premise of their finding is that higher flow rate of central ECMO achieves potentially quicker reversal of shock and multiorgan dysfunction. A recent study by Rambaud et al. showed a survival of 64% among newborns and 50% among pediatric patients in their retrospective study looking at venoarterial ECMO support for neonatal and pediatric refractory septic shock.²⁹ They suggested transferring patients who have oliguria and no decrease in lactate level within 6 hours of maximum drug therapy to ECMO centers.

Performance Bundle

The goal of a performance bundle is to identify and correct barriers that are impeding the attainment of recognition, resuscitation, and stabilization bundle goals. This should contain:

- Measurement of both process and outcome metrics including adherence as well as achievement of goals and individual components of the bundles
- Mechanism to monitor, improve and sustain adherence to best practices.

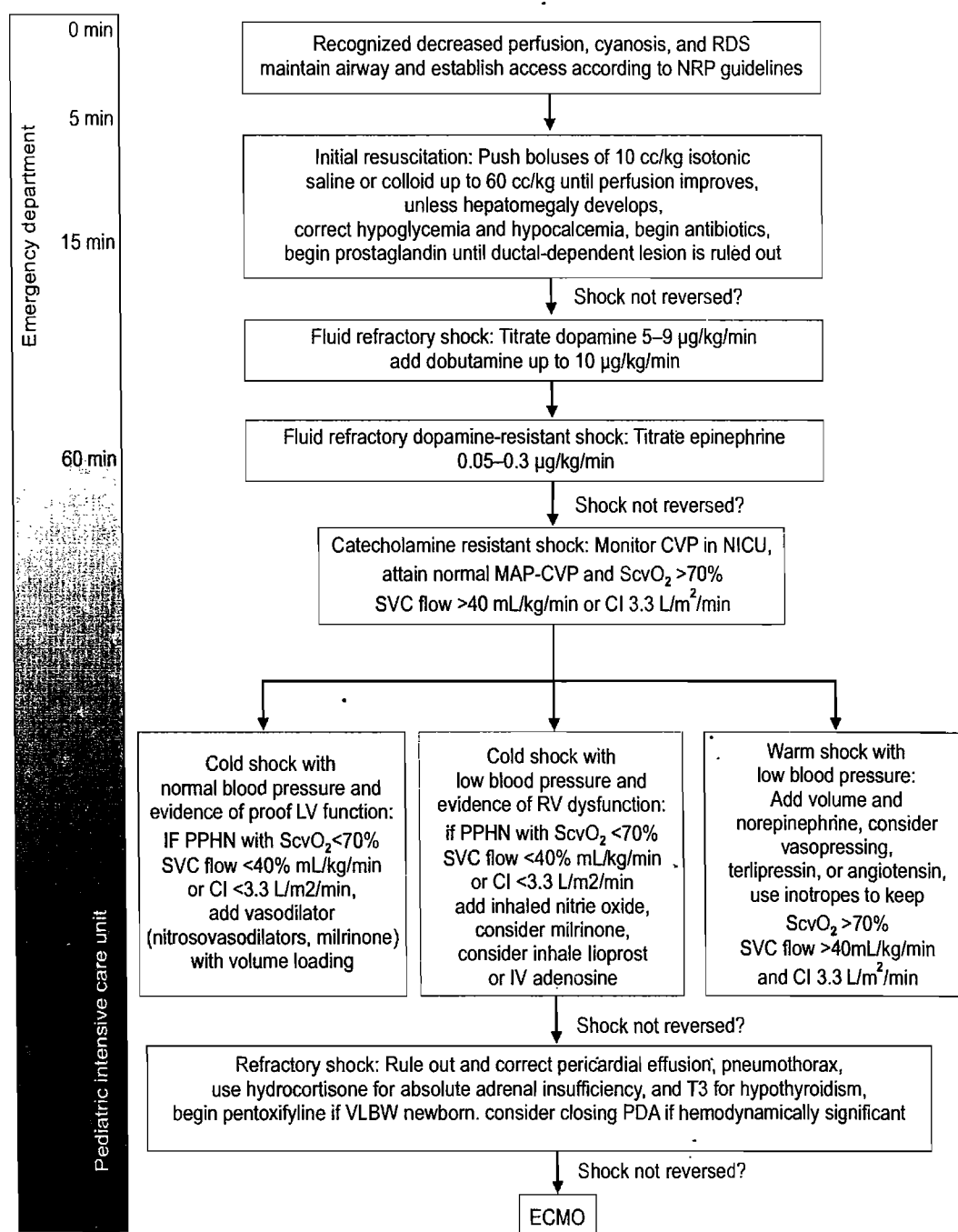


FIG. 4: Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in newborns

Barriers to Implementation of Pediatric Severe Sepsis Guidelines, Obstacles to the Three Bundle Approach, and Suggested Pragmatic Approaches

Three Bundle Approach in Resource-limited Settings

One of the key components of the sepsis bundle is early identification and prompt treatment with intravenous fluid resuscitation. However, a study by Maitland et al. in their Fluid Expansion as Supportive Therapy (FEAST) study found that fluid boluses are significantly associated with increased

48-hour mortality in critically ill febrile children with impaired perfusion who received fluid boluses in resource-limited settings in Africa.³⁰ But most of the participants in this study did not meet the World Health Organization (WHO) criteria for shock (cold hands, capillary-refill longer than 3 seconds, and weak and fast pulse), and their characteristics suggested that they had conditions that would be adversely affected by overhydration (severe anemia, pneumonia, and meningitis).³¹

The FEAST study, suggested training and implementation of triage, basic life support measures, and regular observations as ways to improve survival among critically ill children in the study group.³⁰ In children with suspected malaria or anemia,

the WHO guideline also suggested that fluid be administered cautiously and/or blood transfusion in severe anemia.

Lack of Laboratory Support, Equipment, and Trained Staff in Low- and Middle-income Countries

To ensure adherence to sepsis guidelines and protocols, Musa et al. suggested that guidelines and recommendations should be context dependent.³² They laid out the suggestions and recommendations of the European Society of Intensive Care Medicine's Global Intensive Care Working Group, noting that early identification of critically ill child is a major challenge. They recommended a quality assurance protocol to ensure timely antibiotics administration; fluid management protocol that will be slower depending on the nutritional and clinical status of the patient; oxygen and respiratory support with continuous positive airway pressure or high flow nasal cannula depending on availability; age of the patient; and clinical status, among other things.

Lack of Knowledge and Skills

Kirby et al. noted that there are significant barriers to full implementation of these guidelines by community physicians who might not have the knowledge and skills to recognize and treat septic shock in children.³³ They suggested that for improved outcome from septic shock, there should be clear communication between community physicians and critical care experts/emergency room physicians through the telephone or telemedicine program so that the pediatric patient will receive the best possible care in a timely fashion. Along the same line, a study by Cvetkovic et al. in the United Kingdom showed that over half of the deaths in children referred to the ICU with severe sepsis happened in the first 24 hours of referral, and that 26% of deaths even occurred prior to PICU admission.³⁴ In this regard, quality improvement and educational effort need to be directed to the staff of the hospitals referring critically ill children to the pediatric ICU.

System Issues with Sepsis Identification

Cruz et al. found in their root-cause-analysis that system issues with sepsis identification and management are strong barriers to optimal care of children with sepsis.³⁵ They demonstrated that a computerized triage system that alarmed with abnormal vital signs, toxic appearing or high risk children prompting a chain of resuscitative measures including immediate physician assessment, initiation of sepsis bundles and any other pertinent resources facilitated prompt goal-directed therapy. Their median time from triage to first bolus decreased from 56 minutes to 22 minutes while their median time from triage to first antibiotics decreased from 130 minutes to 38 minutes.

Similarly, studies have shown that adherence to the Pediatric Advanced Life Support Septic Shock guideline is associated with improved outcomes in terms of decreased

length-of-hospital stay, and in cases where there are incomplete adherence to all the components of the guideline, implementation of quality improvement intervention greatly improved adherence.^{36,37}

Lack of Communication and Physician Involvement in Guideline Development

Though some studies have demonstrated improvements in both process metrics (for example decreased time to administration of intravenous fluids, antibiotics, and peripheral vasoactive drugs) and outcome metrics including length of hospital stay, length of PICU stay, and mortality,³⁵⁻³⁸ there are still incomplete adherence to the recommended goals of the administration of intravenous fluids, intravenous antibiotics, and peripheral vasoactive agents. To improve adherence to the guideline, the relevant physicians and policy makers at those institutions should be involved early in the process of crafting the guideline.³⁹

Other Factors Influencing Adherence to Guideline and Outcomes

Simulation of Management of Septic Shock

Simulation of management of pediatric septic shock among residents in pediatric training in the United States improved significantly the residents' performance scores, and repeated simulations showed even more significant ongoing improvement.⁴⁰ This could be applied in any setting.

Similarly, Kessler et al. used a standardized *in situ* scenario across multiple EDs, and found that there is disparity in adherence across these EDs with pediatric EDs following the guideline, more than the general EDs.⁴¹ In this simulation study, they also found that only composite team experience level was associated with improved adherence to the guidelines.

Managing Mortality Predictors and Risk Stratification

Haque et al. demonstrated that high Vasoactive Inotropic Score (VIS) in fluid refractory shock is associated with poor outcome among children in a university hospital in Pakistan.⁴² In their study, mortality rate among children with low VIS was 43% compared to 100% among those with high VIS. Since inotropes are commonly used in shock management, and VIS is easy to calculate, they suggested that VIS could be used as a predictor of outcome in sepsis in resource-limited setting, and consequently be included as one of the components of bundles of predictors of outcome in children with septic shock.

Shock index (SI-ratio of heart rate to the systolic blood pressure) is an easily calculated predictor of mortality, and Rousseaux et al. demonstrated that SI could be used for early recognition of severe sepsis.⁴³ They showed that abnormal SI

at both admission and at 6 hours was predictive of death, and they emphasized that early recognition of sepsis improves outcome.

Acute kidney injury (AKI) in sepsis is associated with worse outcomes, and identification of patients who are at risk of developing AKI in sepsis help to direct their medical care.⁴⁴

Wong et al. derived and tested a multibiomarker-based model for estimating risk of developing AKI in sepsis. This cumulatively adds to the diagnostic tools for timely diagnosis and prompt treatment in septic children.

Increasing Public Awareness of Sepsis

Sepsis is one of the most common causes of death but one of the least recognizable diseases. An international survey showed poor public awareness of the word sepsis in most parts of the world.¹¹ In fulfillment of one of the goals of World Sepsis Day, "raising public and professional awareness and understanding of sepsis", on September 13th 2012, supporters organized over 200 events in all the continents and over 40 countries to raise awareness and educate health workers and the public on the scourge of this health disaster.⁴⁵ These events were extensively covered by the print media and television houses, and public officers and policy makers participated. Similar events are organized every year to mark the World Sepsis Day. We should leverage the use of social media to promote awareness about sepsis ([url:http://www.global-sepsis-alliance.org/](http://www.global-sepsis-alliance.org/)).

Tertiary Prevention: Limited of Disability and Rehabilitation

Addressing Prenatal and other Risk Factors

A study of Swiss extremely premature infants showed that proven sepsis is significantly associated with the development of neurodevelopmental impairment, independent of other risk factors.⁴⁶ A multivariate analysis of their study population showed that proven sepsis independently increased the risk of cerebral palsy. They suggested a strong need for strategies to reduce sepsis in this vulnerable population, which by extrapolation would reduce these long-term disabilities. Similarly, in Senegal, under-five children with bacterial meningitis have more than threefold odds of developing major disability (motor deficit, seizure disorder, visual disturbances, hearing loss, cognitive impairments, etc.), lower quality of life scores and an average total lifetime sequelae of about US \$35,000 per child.^{47,48} Some of this disability could have been prevented with the use of the HIB conjugate vaccine and the meningococcus vaccine.⁴⁷

Addressing Predictors of Functional Outcome

A short-term analysis of pediatric patients with severe sepsis who survived up to 28 days showed diminished functional outcomes; and predictors of poor functional outcome include

history of immune compromise, intra-abdominal and central nervous infections, trauma, higher Pediatric Risk of Mortality (PRISM) III score, and Hispanic origin.⁴⁹ Farris et al. suggested that these predictors of poor functional outcomes are also points of interventions to improve outcomes in this regards.

Addressing Predictors of Postdischarge Mortality

It is known that patients who have not returned fully to be their prehospitalization baseline prior to discharge have increased risk of rehospitalization and increased mortality. Consequently, identification of these at high-risk group of patient would prompt postdischarge plan that might include home nursing visit and early postdischarge follow-up visits.

Wiens et al. in their work at a Ugandan hospital developed a postdischarge risk prediction model using five simple measurable variables including mid-upper arm circumference, time since last hospitalization, oxygen saturation, abnormal Blantyre Coma Scale score, and HIV-positive status.⁵⁰ This model helps to improve discharge planning for the identified high risk patients, according to them. Similarly, Gambian children who are malnourished, as defined by Mid-Upper Arm Circumference (MUAC) are at increased risk of postdischarge mortality.⁵¹ Very importantly, they found in this study that in addition to children who are severely malnourished (MUAC <11.5 cm), those who are moderately malnourished (MUAC 11.5–13.0 cm) have about sevenfold increase in postdischarge mortality. They advised preventive measures including nutritional rehabilitation and close follow-up of these at risk malnourished children.

CONCLUSION

Pediatric severe sepsis is a devastating clinical and public health urgency with debilitating and often long-lasting health, social, and economic consequences. It is a disease spectrum that is so common yet so unknown even among health workers, and the lay population.

The key element in improving sepsis outcomes rests on recognition and prompt treatment in a way that addresses the key pathophysiological derangement of this syndrome first, but narrowing care to the particular disease entity (bacterial, viral, and protozoal) leading up to the clinical features of severe sepsis. We also highlighted the need to approach sepsis management in a very comprehensive manner including all levels of prevention.

Lastly, we would encourage every effort to increase awareness about this gigantic, preventable, and treatable disease spectrum, among healthcare workers, policy makers, and the public in general.

REFERENCES

1. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6:2-8.

2. Kissoon N, Uyeki TM. Sepsis and the global burden of disease in children. *JAMA Pediatr.* 2016;170:107-8.
3. Kissoon N, Daniels R, van der Poll T, et al. Sepsis—the final common pathway to death from multiple organ failure in infection. *Crit Care Med.* 2016;44:e446.
4. Kissoon N, Carcillo JA, Espinosa V, et al. World Federation of Pediatric Intensive Care and Critical Care Societies: Global Sepsis Initiative. *Pediatr Crit Care Med.* 2011;12:494-503.
5. Schlapbach LJ, Straney L, Alexander J, et al. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. *Lancet Infect Dis.* 2015;15:46-54.
6. Thompson GC, Kissoon N. Sepsis in Canadian children: a national analysis using administrative data. *Clin Epidemiol.* 2014;6:461-9.
7. Folgori L, Livadiotti S, Carletti M, et al. Epidemiology and clinical outcomes of multidrug-resistant, Gram-negative bloodstream infections in a European tertiary pediatric hospital during a 12-month period. *Pediatr Infect Dis J.* 2014;33:929-32.
8. Ganjoo S, Ahmad K, Qureshi UA, et al. Clinical Epidemiology of SIRS and Sepsis in Newly Admitted Children. *Indian J Pediatr.* 2015;82:698-702.
9. Wang Y, Sun B, Yue H, et al. An epidemiologic survey of pediatric sepsis in regional hospitals in China. *Pediatr Crit Care Med.* 2014;15:814-20.
10. Erratum: Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study. *Am J Respir Crit Care Med.* 2016;193:223-4.
11. Rubulotta FM, Ramsay G, Parker MM, et al. An international survey: Public awareness and perception of sepsis. *Crit Care Med.* 2009;37:167-70.
12. Yipp BG, Winston BW. Sepsis without SIRS is still sepsis. *Ann Transl Med.* 2015;3:294.
13. Wiens MO, Larson CP, Kumbakumba E, et al. Application of sepsis definitions to pediatric patients admitted with suspected infections in Uganda. *Pediatr Crit Care Med.* 2016;17:400-5.
14. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti Infect Ther.* 2011;9:71-9.
15. Siqueira-Batista R, Mendonca EG, Gomes AP, et al. Proteomic updates on sepsis. *Rev Assoc Med Bras.* 2012;58:376-82.
16. Wiens MO, Kumbakumba E, Kissoon N, et al. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. *Clin Epidemiol.* 2012;4:319-25.
17. Pavare J, Grope I, Gardovska D. Prevalence of systemic inflammatory response syndrome (SIRS) in hospitalized children: a point prevalence study. *BMC Pediatr.* 2009;9:25.
18. Raihana S, Dunsmuir D, Huda T, et al. Development and internal validation of a predictive model including pulse oximetry for hospitalization of under-five children in Bangladesh. *PLoS One.* 2015;10:e0143213.
19. Riley C, Wheeler DS. Prevention of sepsis in children: a new paradigm for public policy. *Crit Care Res Pract.* 2012;2012:437139.
20. Carcillo JA. Reducing the global burden of sepsis in infants and children: a clinical practice research agenda. *Pediatr Crit Care Med.* 2005;6:S157-64.
21. Roth A, Jensen H, Garly ML, et al. Low birth weight infants and Calmette-Guérin bacillus vaccination at birth: community study from Guinea-Bissau. *Pediatr Infect Dis J.* 2004;23:544-50.
22. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. *Pediatrics.* 2004;114:e565-71.
23. Cohen J, Chin W. Nutrition and sepsis. *World Rev Nutr Diet.* 2013;105:116-25.
24. Chisti MJ, Salam MA, Bardhan PK, et al. Severe Sepsis in Severely Malnourished Young Bangladeshi Children with Pneumonia: A Retrospective Case Control Study. *PLoS One.* 2015;10:e0139966.
25. Khanal S, Sharma J, GC VS, et al. Community health workers can identify and manage possible infections in neonates and young infants: MINI—a model from Nepal. *J Health Popul Nutr.* 2011;29:255-64.
26. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med.* 2009;37:666-88.
27. Ruth A, McCracken CE, Fortenberry JD, et al. Extracorporeal therapies in pediatric severe sepsis: findings from the pediatric health-care information system. *Crit Care.* 2015;19:397.
28. MacLaren G, Butt W, Best D, et al. Central extracorporeal membrane oxygenation for refractory pediatric septic shock. *Pediatr Crit Care Med.* 2011;12:133-6.
29. Rambaud J, Guellec I, Leger PL, et al. Venoarterial extracorporeal membrane oxygenation support for neonatal and pediatric refractory septic shock. *Indian J Crit Care Med.* 2015;19:600-5.
30. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364:2483-95.
31. Duke T. What the African fluid-bolus trial means. *Lancet.* 2011;378:1685-7.
32. Musa N, Murthy S, Kissoon N. Pediatric sepsis and septic shock management in resource-limited settings. *Intensive Care Med.* 2016.
33. Kirby A, Goldstein B. Improved outcomes associated with early resuscitation in septic shock: do we need to resuscitate the patient or the physician? *Pediatrics.* 2003;112:976-7.
34. Cvetkovic M, Lutman D, Ramnarayan P, et al. Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. *Pediatr Crit Care Med.* 2015;16:410-7.
35. Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics.* 2011;127:e758-66.
36. Paul R, Melendez E, Stack A, et al. Improving adherence to PALS septic shock guidelines. *Pediatrics.* 2014;133:e1358-66.
37. Paul R, Neuman MI, Monuteaux MC, et al. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. *Pediatrics* 2012;130:e273-80.
38. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics* 2011;127:e1585-92.
39. Kissoon N. Sepsis guidelines: Suggestions to improve adherence. *J Infect.* 2015;71:S36-41.
40. Dugan MC, McCracken CE, Hebbard KB. Does simulation improve recognition and management of pediatric septic shock, and if one simulation is good, is more simulation better? *Pediatr Crit Care Med.* 2016;17:605-14.
41. Kessler DO, Walsh B, Whitfill T, Gangadharan S, et al. Disparities in adherence to pediatric sepsis guidelines across a Spectrum of Emergency Departments: A multicenter, cross-sectional observational in situ simulation study. *J Emerg Med.* 2016;50:403-15.e3.
42. Haque A, Siddiqui NR, Munir O, et al. Association between vasoactive-inotropic score and mortality in pediatric septic shock. *Indian Pediatr.* 2015;52:311-3.
43. Rousseau J, Grandbastien B, Dorkenoo A, et al. Prognostic value of shock index in children with septic shock. *Pediatr Emerg Care.* 2013;29:1055-9.
44. Wong HR, Cvijanovich NZ, Anas N, et al. A multibiomarker-based model for estimating the risk of septic acute kidney injury. *Crit Care Med.* 2015;43:1646-53.
45. Reinhart K, Daniels R, Machado FR; World Sepsis Day Steering Committee and the Global Sepsis Alliance Executive Board. The burden of sepsis: a call to action in support of World Sepsis Day 2013. *Rev Bras Ter Intensiva.* 2013;25:3-5.
46. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics.* 2011;128:e348-57.
47. Edmond K, Dieye Y, Griffiths UK, et al. Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. *Pediatr Infect Dis J.* 2010;29:1023-9.
48. Griffiths UK, Dieye Y, Fleming J, et al. Costs of meningitis sequelae in children in Dakar, Senegal. *Pediatr Infect Dis J.* 2012;31:e189-95.
49. Farris RW, Weiss NS, Zimmerman JJ. Functional outcomes in pediatric severe sepsis: further analysis of the researching severe sepsis and organ dysfunction in children: a global perspective trial. *Pediatr Crit Care Med.* 2013;14:835-42.
50. Wiens MO, Kumbakumba E, Larson CP, et al. Postdischarge mortality in children with acute infectious diseases: derivation of postdischarge mortality prediction models. *BMJ Open.* 2015;5:e009449.
51. Chhibber AV, Hill PC, Jafali J, Jasseh M, et al. Child mortality after discharge from a health facility following suspected pneumonia, meningitis or Septicaemia in rural Gambia: A Cohort Study. *PLoS One.* 2015;10:e0137095.

Fluid Balance: Where are We Going with Fluids and Electrolytes in the Pediatric Intensive Care Unit?

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INTRODUCTION

For many years, fluid therapy in the pediatric intensive care unit (PICU) was based on the assumptions that boluses of fluid were appropriate for the management of shock in a variety of settings, and that the recommendations of Holliday and Segar¹ were appropriate for volumes of maintenance fluids in the PICU.

More recently, these assumptions have been challenged by the outcomes of the Fluid Expansion as Supportive Therapy (FEAST) study² (showing that pyrexial children with features of hemodynamic instability had worse outcomes with fluid boluses); data showing that children who developed positive fluid balances while in PICU had worse outcomes;³ data showing that even mild-to-moderate dysnatremia in the adult intensive care unit (ICU) was associated with worse outcomes;^{4,5} and data showing that children were dying in hospitals as a result of iatrogenic hyponatremia.⁶

Some of the particular challenges of the PICU as regards fluids and electrolytes include the following:

- There are a wide range of patients seen in PICU and the fluid and electrolyte requirements in these patients may differ considerably depending on factors such as pathology (consider patients with large body surface area burns vs. patients following brain surgery), age (preterm infants vs. adolescents); previous therapy, and ongoing therapy (e.g., need for diuretic therapy and need for hydration for chemotherapy)
- Many patients in the PICU have single- or multiorgan failure and this/these dysfunction(s) may have multiple effects on fluid requirements and fluid balances
- The balance of fluid and electrolytes depends on the interaction between the patient (their physiological and pathological processes); the fluids and electrolytes that are administered to those patients (including fluids, feeds, medication—even just the diluents provided with medications); multiple potential sites of fluid loss (including drains, catheters and dialysis therapy); the

medications and therapies (such as administration of blood and coagulation products) administered to those patients; the use of organ support therapies (including mechanical ventilation and renal replacement therapy)

- The duration of stay in PICU may be extremely variable and the fluid and electrolyte balances are likely to change during that stay as the condition of the patient changes.

The counterpoint to these challenges is that the environment in the PICU is such that it is possible to accurately measure and monitor fluid and electrolyte balance in most patients, and use that information to adjust therapy to ensure achievement of appropriate goals.

While this review will focus on the fluid and electrolyte balance in critically patients, it is important to consider that fluid balances may have profound effects on other issues such as drug levels and bioavailability of those agents. In addition protein content of fluids may have significant effects on the bioavailability of medication such as antibiotics.⁷

FLUIDS FOR RESUSCITATION

There are groups of patients where the rapid administration of intravascular fluids is lifesaving. There is little argument that administration of fluids and electrolytes (such as 0.9% saline or Ringer's lactate) in bolus form may be helpful to the child who has rapidly lost fluids and electrolytes from the intravascular space as a result of severe gastroenteritis. There is little argument over the need for blood products in patients with active bleeding and hypovolemia.

Sepsis

Some years ago there was strong agreement that fluid boluses were an important component of resuscitation (particularly in sepsis),⁸ and current guidelines on resuscitation for severe sepsis in children recommend the administration of up to 60 mL/kg of fluids within the first hour of presentation to the emergency department or PICU⁹ (less, if there is an

appropriate clinical response to resuscitation). A number of studies have shown that compliance with this approach is associated with improved outcomes.¹⁰ In India, another study showed no difference in outcomes between children with septic shock given a rapid fluid bolus (40 mL/kg of fluid over 15 min) versus slower fluid administration (20 mL/kg over 20 min up to a maximum of 60 mL/kg over 1 h) together with titrated inotropic therapy.¹¹ Perhaps significantly, there was increased hepatomegaly detected in those children given the more rapid fluid bolus.

There is also evidence from a large study involving over 3,000 children in East Africa that fluid bolus administration may be deleterious in sick children,² with increased mortality associated with bolus therapy despite initial "improvement" with the therapy. That study involved a large group of children, many of whom had additional underlying problems such as malaria and anemia. Intensive care support was not available to these children, and so there has been considerable debate concerning the implications of this study for the management of children with severe sepsis in other settings.

The assumption has been made that in shocked children with sepsis there are common features such as reduced cardiac output; altered vascular (both arterial and venous) tone; poor tissue perfusion and decreased oxygen delivery (with resultant organ damage), and consequent multiorgan dysfunction.¹² However, there is recent data showing that the hemodynamics in children with severe sepsis may vary substantially^{13,14} and although some children may have low-cardiac output, the reverse may be true in others. In addition, while the assumption has been made that reduced organ perfusion is deleterious, it is possible that reduced perfusion may be protective in some circumstances by mechanisms such as reduced washout of potentially "toxic" products such as inflammatory cytokines.¹⁵ Thus, it is likely that while some children will respond positively to a bolus of fluids, there are others who may suffer adverse consequences.

In addition, even if there is low-cardiac output in a patient it is not clear whether administration of a bolus of fluid will increase cardiac output. The effect of a fluid bolus on cardiac output will depend on a complex interaction between vascular tone (both arterial and venous); cardiac contractility and rate, and intravascular volumes. Depending on the intersection of several interrelated physiological curves administration of fluid to an individual, patient may result in increased, decreased, or unchanged cardiac output.¹² Unfortunately, clinical measures of cardiac output in critically ill children are unreliable^{16,17} and current predictors of the effect of a fluid bolus on the hemodynamics of an individual child are also unreliable.¹⁸⁻²⁰ There are ongoing studies investigating the possibility of prediction of the response to fluid bolus administration in severe sepsis in children.²¹

Although there is limited information regarding the optimal volumes of fluids for resuscitation in children, it

is clear that underlying disease processes need to be taken into account. As an example, children on chemotherapy may have disordered cardiac function related to that medication, and if they develop sepsis this would have to be taken into account when considering fluid bolus therapy. Underlying anemia may be effectively exacerbated by vigorous fluid administration. Although concerns about the impact of malnutrition on the responses to fluid therapy are frequently expressed, there is very little data to underpin these concerns.^{22,23}

Related to concerns about the impact of bolus therapy on outcomes, the fact that fluid accumulation in critically ill children is associated with increased respiratory problems^{3,24,25} and increased mortality in children requiring renal replacement therapy.²⁶

A recent recommendation from the International Liaison Committee on Resuscitation (ILCOR)²⁷ suggested that resuscitation for severe sepsis with shock should start with volumes of 20 mL/kg with review of clinical responses. This would seem reasonable, and it is also important to note that during the course of PICU stay the hemodynamics of patients admitted with fluid refractory septic shock may change, with varying requirements for additional fluid therapy and/or inotropic therapy.²⁸ Thus, ongoing therapy should be guided by clinical responses together with careful monitoring of both hemodynamics and fluid balance.

Dengue

In the setting of dengue with shock, administration of fluids boluses of approximately 20 mL/kg is associated with a significant improvement in mortality,²⁹ and there are concerns about possible adverse effects from larger volumes.

Trauma

In the trauma setting, recent recommendations for fluid resuscitation suggest a more conservative approach with volumes of 10 mL/kg per bolus until bleeding is controlled,³⁰ and there is animal evidence that the stepwise administration of small volumes of resuscitation fluids (vs. bolus therapy) may be associated with improved outcomes.³¹ Critically ongoing bleeding in trauma requires transfusion of blood, and may require the implementation of "massive transfusion" guidelines, which would include coagulation products such as platelets and plasma. The use of tranexamic acid is also recommended in these patients to limit bleeding.

Burns

There is a growing realization that many patients with severe burns were suffering significant complications that could be directly attributed to excessive fluid resuscitation and maintenance.³² Clearly, this may be related to overestimation of the burn size which may happen commonly.³³ Thus,

although fluids are clearly required for resuscitation, care must be exercised to avoid administration of excess.

Choice of Fluids for Resuscitation

There has been considerable discussion on the relative merits of different fluids given for resuscitation. In principle, the electrolyte content of resuscitation fluids should not be too different from that of plasma, and there is agreement that glucose should not be added to resuscitation fluids. Although there has been controversy on the relative benefits of colloids (fluids with large molecular weight molecules such as albumin or synthetic molecules suspended in a crystalloid solution) versus crystalloid solutions, there is little evidence for both adults and children that the use of (more expensive) colloids for resuscitation is associated with lower mortality than the use of crystalloid solutions.^{2,34,35}

The content of fluids commonly utilized for resuscitation is shown in table 1.

Crystalloids

Some of the benefits associated with crystalloids are the relatively low cost of manufacture and the lack of

specialized storage requirements such as refrigeration. The most commonly used crystalloid is 0.9% saline (so-called "normal" saline). However, there is growing evidence that 0.9% saline may not be the optimal fluid for resuscitation as administration is associated with problems such as hyperchloremic metabolic acidosis.³⁶ "Balanced salt solutions" and Ringers lactate may be preferable to 0.9% saline for resuscitation in both septic shock and diabetic ketoacidosis.³⁷

Hypertonic saline has been studied as a possible alternative to 0.9% saline in septic shock, but does not appear to have significant advantages.³⁸ There is one reported study in patients following cardiac surgery that hyperoncotic and hypertonic fluids were associated with improved hemodynamics.³⁹

Colloids

Colloids rather than crystalloids have been recommended for resuscitation on the basis that lower volumes would be required for resuscitation and those volumes would stay within the intravascular space for longer than crystalloids. Both of these reasons may be inaccurate as although a volume ratio of 1:3 has been described for colloids versus

TABLE 1 Content and characteristics of commonly used intravenous fluids (human plasma data put in for comparison)

Solution	Osmolality (mOsmol/L)	Sodium (mmol/L)	Chloride (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)	Glucose (mmol/L)	Other (mmol/L)
Human plasma	291	135–145	94–111	4.5–5.0	2.2–2.6	–	Magnesium 0.8–1.0, lactate 1–2, bicarbonate 23–27
<i>Resuscitation</i>							
Sodium chloride 0.9%	308	154	154	–	–	–	–
Ringer's lactate solution	280	131	111	5.4	2.0	–	Lactate 29
4% human albumin solution (this can vary in electrolyte content across the world with different producers)	250	140	128	–	–	–	Octenoate 6.4
Plasmalyte B	291	140	98	5	–	–	Magnesium 3, acetate 27, gluconate 23
<i>Maintenance</i>							
Sodium chloride 0.9% and glucose 5%	586	150	150	–	–	27.78	–
Sodium chloride 0.45%	154	77	75	–	–	0	–
Sodium chloride 0.45% and glucose 5%	432	75	75	–	–	27.78	–
Sodium chloride 0.45% and glucose 2.5%	293	75	75	–	–	13.89	–
Half-strength Darrow's with glucose 5%	434	61	52	17	–	27.78	Lactate
Sodium chloride 0.18% and glucose 4%	284	31	31	–	–	22.22	–
Glucose 5%	278	0	–	–	–	27.78	–
Glucose 10%	555	0	–	–	–	55.55	–

crystalloids⁴⁰ in practice this may be closer to 1:1.3.⁴¹ Likewise, fluid leak from the intravascular space is related not only to pressure gradients (oncotic and hydrostatic) but also to dysfunction of the glycocalyx.⁴²

A recent systematic review³⁴ showed no benefit in outcomes from colloids versus crystalloids in the initial management of children with severe sepsis or septic shock.

Recent evidence suggests that there is little place for the use of synthetic colloids in critically ill children as they are relatively expensive, they are associated with adverse effects on coagulation and renal function, and the long-term effects in children have not been well characterized.

As long ago as 1998 concerns were raised about the use of human albumin for resuscitation in adult patients.⁴³ Since that time a number of studies have shown that the use of albumin rather than saline for resuscitation may have worsened the outcomes of patients with traumatic brain injury;⁴⁴ that there was no difference in outcomes or organ dysfunction between patients with septic shock resuscitated with 0.9% saline or 4.5% albumin⁴⁵ (there may be some benefit associated with the use of albumin); and that burns patients resuscitated with albumin may have had higher mortality.⁴⁶ In hypotensive neonates, resuscitation with albumin was associated with increased return to normotension and less subsequent use of inotropes than 0.9% saline.⁴⁷

Thus, there are no indications for the use of synthetic colloids in the PICU; there may be some benefits in some groups of patients related to albumin usage (but this must be offset by the significant costs relative to crystalloids), but

there is no clear indication to prefer albumin over crystalloids in most patients.

A recent consideration has been the effect of albumin administration on the availability of medication such as antibiotics.⁷

Blood Products

Blood products such as packed red cells, fresh frozen plasma, and cryoprecipitate may often be utilized as part of the resuscitation of critically ill children. However, all of these products are expensive, and their use is associated with significant side effects. They should only be used, if there are clear indications for their use.

Maintenance Fluids

The term "maintenance fluids" is commonly used to imply the normal fluid requirements of a patient. However, in the critical care environment it may be more appropriate to refer to "the volume of fluid required to maintain the current fluid balance of this patient". Critically, the amount of fluid administered to a patient should be related to the fluid losses of that patient (Tables 2 and 3 for inputs and outputs to be considered in the PICU).

Fluids and electrolytes are clearly very closely related as changes in either fluid or electrolyte balance (or both) will have consequences for electrolyte concentrations throughout the body.

TABLE 2 Fluid and electrolyte inputs to be specifically considered in the pediatric intensive care unit (in addition to "maintenance fluids")

Category	Challenges	Responses
Enteral feeds	<ul style="list-style-type: none"> Cannot be entirely sure of what proportion of feed will actually be absorbed by the patient 	–
Vasoactive drugs	<ul style="list-style-type: none"> Constant infusions May be varied during the PICU stay and particularly initially may be substantially altered 	<ul style="list-style-type: none"> May have to adjust drug concentration to limit water intake May be made up with different diluents
Blood and coagulation products	<ul style="list-style-type: none"> These products are sometimes required in order to optimize hemoglobin concentrations and control bleeding problems 	<ul style="list-style-type: none"> Planning of possible use of these products during the day may enable the clinician to limit other fluids and achieve reasonable fluid balance
Sedation and analgesia	<ul style="list-style-type: none"> Often constant infusions 	<ul style="list-style-type: none"> Can give medication orally and reduce infusion volumes Can increase concentration of medication May have different diluents
Antibiotics	<ul style="list-style-type: none"> Fluid administration volumes have to be included in all fluid balance documentation 	<ul style="list-style-type: none"> May be possible to adjust the concentrations of the medication
Infusion systems	<ul style="list-style-type: none"> This would include the flushes on central lines and arterial lines Intravenous fluids Enteral feeds 	<ul style="list-style-type: none"> Hypernatremia has been described related to saline containing medication infusions⁴⁸

PICU, pediatric intensive care unit.

TABLE 3 Fluid and electrolyte outputs to be specifically considered

Category	Challenges	Responses
Drain losses	<ul style="list-style-type: none"> May contain high protein losses (particularly pleural drains with chylous effusions) 	<ul style="list-style-type: none"> Measurement of volume and electrolyte content of losses may assist in planning of replacement therapy
Urine output	<ul style="list-style-type: none"> May be substantial variation in urine output during the course of the PICU stay, particularly if acute kidney injury May be substantial variation in electrolyte content (ranging from very low in diabetes insipidus through to very high with salt wasting) 	<ul style="list-style-type: none"> Measurement of volume and electrolyte content of losses may assist in planning of replacement therapy
Nasogastric losses	<ul style="list-style-type: none"> May be substantial (particularly in the setting of surgical intra-abdominal problems) 	<ul style="list-style-type: none"> Possible to measure both volumes and electrolyte contents In the setting of jejunal tubes, may be possible to put gastric losses back into the jejunum
Stool losses (can include stoma losses in this category)	<ul style="list-style-type: none"> May be negligible, but may also be very substantial May be more difficult to measure 	<ul style="list-style-type: none"> In the setting of stoma losses, it may sometimes be appropriate to return stoma losses into distal mucus fistulae
Renal replacement therapies	<ul style="list-style-type: none"> Dialysis (peritoneal or hemodialysis) or hemofiltration 	<ul style="list-style-type: none"> These losses are usually very tightly controlled, but that may not be true in peritoneal dialysis During renal replacement therapy, but may be possible to maintain glucose levels using the dialysis technique and thus stop infusions required to maintain glucose levels
Skin losses	<ul style="list-style-type: none"> Although these are generally very low, there may be very high salt losses (as in cystic fibrosis) or very high water losses (burns and some congenital skin abnormalities) 	<ul style="list-style-type: none"> Virtually impossible to measure fluid losses Can be limited by ensuring appropriate surrounding humidification

PICU, pediatric intensive care unit.

While many critically ill children have limited fluid losses (particularly those with renal failure or high-antidiuretic hormone levels), there are patients such as those with diarrhea, renal disease, extensive skin disease (including burns), or substantial drain losses where fluid losses may be extremely large and in these children there is the dual challenge of replacement of losses with equivalent volumes of fluid and electrolyte content and provision of normal "maintenance fluids". In the context of dehydration, it may be appropriate to administer fluid in excess of daily losses in order to replace dehydration, but in many patients it may be important to ensure that less fluid is administered than is lost in order to allow the loss of excess fluid.

The challenge (particularly in smaller infants) is that the clinician is required to administer enough glucose to maintain glucose levels; enough calories to prevent the development of catabolic states; enough electrolytes to avoid electrolyte imbalance; medication (some medications require significant diluents in order to allow safe administration, and some medications are given as continuous infusions). Thus, considerable attention needs to be paid to the nature and volume of fluids given as an accompaniment to nutrition and medication (Table 4). In fact, where possible maintenance fluids should be administered enterally with appropriate feeds and fluids.⁴⁹

TABLE 4 Electrolyte concentrations throughout the body⁵²

Electrolyte	Intracellular concentration (mmol/L)	Extracellular concentration (mmol/L)	Plasma concentration (mmol/L)
Sodium (Na ⁺)	15	143	141
Potassium (K ⁺)	140	4	4
Chloride (Cl ⁻)	8	115	103
Calcium (Ca ⁺⁺)	0.0001	1.3	2.5
Bicarbonate (HCO ⁻)	15	28	25
Magnesium (Mg ⁺⁺)	15	0.7	1
Phosphate (PO ₄ ⁻)	10 L	1	1

ELECTROLYTE BALANCE AND CONCENTRATIONS

Electrolytes are not evenly distributed throughout the body compartments and the concentration of those electrolytes is shown in table 4. There are substantial differences between the intra- and extracellular concentrations of important

electrolytes, and even between interstitial and intravascular concentrations. Changes in the absolute and relative concentrations of these electrolytes may cause substantial changes in osmolality across cell membranes, and be associated with significant complications. The dominant electrolytes are sodium (Na), potassium (K), and chloride and the discussion will focus primarily on these electrolytes.

Sodium

Sodium is the dominant extracellular ion and dysnatremia (where Na levels are outside the normal range) is relatively common in sick children and may have profound consequences, with major impact on the brain. There is evidence that even relatively mild dysnatremia may be associated with increased morbidity in sick adults;⁴ moderate-to-severe dysnatremia has been associated with brain injury and death in children;⁵⁰ and correction of dysnatremia has been shown to improve outcomes in adults.⁵¹

Patients may be admitted to the PICU with dysnatremia as a consequence of previous disease (gastroenteritis, diabetes insipidus, etc.) or may develop dysnatremia while in the PICU as a consequence of inappropriate administration of fluids—both in volume and in electrolyte content. In general, patients with excessive loss of fluids are at increased risk of hypernatremia, while those with excessive fluid administration (or retention of fluid) are more at risk of hyponatremia.

Fluid and electrolyte losses from the body will depend on the site of the losses. The Na contents of saliva and gastric fluids range between 60 and 80 mmol/L, while small bowel contents and fluid from the bile duct range from 120 to 140 mmol/L.⁵² While glomerular filtrate is generally about 140 mmol/L in health, the Na content of urine can range between 1 and 300 mmol/L⁵² depending on the physiological situation (under the influence of hormones such as aldosterone). Thus, the relative risks of hypo- and hypernatremia can be predicted depending on particular fluid losses.

Since the 1950s, recommended intravenous fluid volumes and Na content were based on the work of Holliday and Segar.¹ However, since the 1990s there has been increasing recognition that children with a wide range of conditions^{53,54} are at risk of hyponatremia when given intravenous fluids, and this is related to both the volume of fluids and the electrolyte content of those fluids. The underlying physiology in many situations probably relates to high levels of antidiuretic hormone⁵⁵⁻⁵⁷ (the capacity to retain fluid during illness or injury would presumably carry a strong evolutionary advantage in environments without intravenous access). Intravenous fluids with high free-water content will also add to the risks of developing hyponatremia.

Current recommendations for maintenance fluids in sick children suggest the use of volumes 50–70% of those

predicted by Holliday and Segar, and the use of isotonic fluids (essentially those with Na concentrations close to those of plasma).⁴⁹

Together with close attention to fluid and electrolyte administration and losses, monitoring of patients with significant volumes of intravenous fluid administration should include regular measurement of serum electrolyte levels⁵⁸ with appropriate adjustment of both fluid volumes and electrolyte content.

Potassium

Although potassium is the major intracellular anion it is found in relatively low concentrations in the extracellular space. Many intravenous fluids given in the PICU have tended to have low-potassium concentrations in view of the concerns related to hyperkalemia (particularly in patients who may have disordered renal function). However, many patients do develop hypokalemia on these fluids⁴⁹ and it may be appropriate to increase the potassium content of fluids once hyperkalemia has been excluded.

Chloride

Chloride levels are usually in balance with sodium, but the concentrations in the extracellular fluid are substantially lower than that of sodium. Increase in chloride levels relative to sodium will be associated with the development of metabolic acidosis (while reductions such as happen with diuretic therapy may be associated with alkalosis). A concern with the use of fluids with equal concentrations of sodium and chloride is that this is associated with the development of metabolic acidosis.

CONCLUSION

Where possible, fluids should be given to (even) critically ill children via the enteral route. However, where this is not possible it is important to carefully monitor fluid balance (as both dehydration and fluid overload are associated with worsened outcomes). Isotonic fluids are generally utilized for resuscitation, but increasing evidence suggests that this may also be appropriate for fluid maintenance. Replacement of fluid losses should take into account the electrolyte content of the fluids that are being lost. Finally, if significant volumes of intravenous fluids are administered to sick children, it is essential to carefully monitor the levels of electrolytes such as sodium and chloride. Remarkably, we still have large gaps in our understanding of how fluids should optimally be used for resuscitation in a wide variety of settings. Future research will have to address these concerns. However, given the complexity of pathophysiology related to conditions such as sepsis, and the range of responses possible to a wide range of pathogens, it seems unlikely

that fluids are the “magic bullet”, and more likely that fluid therapy during resuscitation will need to be tailored to the needs and responses of individual patients.

REFERENCES

- Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19:823-32.
- Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364:2483-95.
- Arikan AA, Zappitelli M, Goldstein SL, et al. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012;13:253-8.
- Darmon M, Diconne E, Souweine B, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. *Crit Care*. 2013;17:R12.
- Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med*. 2010;36:304-11.
- Achinger SG, Moritz ML, Ayus JC. Dysnatremias: why are patients still dying? *South Med J*. 2006;99:353-62; quiz 63-4.
- Brink AJ, Richards GA, Lautenbach EE, et al. Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis. *Int J Antimicrob Agents*. 2015;45:647-51.
- Carcillo JA, Tasker RC. Fluid resuscitation of hypovolemic shock: acute medicine's great triumph for children. *Intensive Care Med*. 2006;32:958-61.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39:165-228.
- de Oliveira CF, de Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive care medicine*. 2008;34:1065-75.
- Santhanam I, Sangareddi S, Venkataraman S, et al. Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. *Pediatr Emerg Care*. 2008;24:647-55.
- Long E, Duke T. Fluid resuscitation therapy for paediatric sepsis. *J Paediatr Child Health*. 2016;52:141-6.
- Brierley J, Peters MJ. Distinct hemodynamic patterns of septic shock at presentation to pediatric intensive care. *Pediatrics*. 2008;122:752-9.
- Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study*. *Pediatr Crit Care Med*. 2014;15:e17-26.
- Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. *Crit Care*. 2012;16:302.
- Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. *Arch Dis Child*. 1999;80:163-6.
- Tibby SM, Hatherill M, Marsh MJ, et al. Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child*. 1997;77:516-8.
- Saxena R, Durward A, Steeley S, et al. Predicting fluid responsiveness in 100 critically ill children: the effect of baseline contractility. *Intensive Care Med*. 2015;41:2161-9.
- Gan H, Cannesson M, Chandler JR, et al. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg*. 2013;117:1380-92.
- Weber T, Wagner T, Neumann K, et al. Low predictability of three different noninvasive methods to determine fluid responsiveness in critically ill children. *Pediatr Crit Care Med*. 2015;16:e89-94.
- Long E, Oakley E, Babi FE, et al. An observational study using ultrasound to assess physiological changes following fluid bolus administration in paediatric sepsis in the emergency department. *BMC Pediatr*. 2016;16:93.
- Obonyo N, Maitland K. Fluid management of shock in severe malnutrition: what is the evidence for current guidelines and what lessons have been learned from clinical studies and trials in other pediatric populations? *Food Nutr Bull*. 2014;35:S71-8.
- Silverman JA, Chimalizeni Y, Hawes SE, et al. The effects of malnutrition on cardiac function in African children. *Arch Dis Child*. 2016;101:166-71.
- Sinitsky L, Walls D, Nadel S, et al. Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. *Pediatr Crit Care Med*. 2015;16:205-9.
- Valentine SL, Sapru A, Higerson RA, et al. Fluid balance in critically ill children with acute lung injury. *Crit Care Med*. 2012;40:2883-9.
- Selewski DT, Cornell TT, Lombel RM, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. *Intensive Care Med*. 2011;37:1166-73.
- Maconochie IK, de Caen AR, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2015;95:e147-68.
- Deep A, Goonasekera CD, Wang Y, et al. Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. *Intensive Care Med*. 2013;39:1602-9.
- Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis*. 2001;32:204-13.
- Group ALS. Advanced Paediatric Life Support: a Practical Approach to Emergencies. 6th edition. Chichester, UK: John Wiley and Sons; 2016.
- Sillescu M, Jin G, Johansson PI, et al. Resuscitation speed affects brain injury in a large animal model of traumatic brain injury and shock. *Scand J Trauma Resusc Emerg Med*. 2014;22:46.
- Ahms KS. Trends in burn resuscitation: shifting the focus from fluids to adequate endpoint monitoring, edema control, and adjuvant therapies. *Crit Care Nurs Clin North Am*. 2004;16:75-98.
- Sadideen H, D'Asta F, Moiem N, et al. Does Overestimation of Burn Size in Children Requiring Fluid Resuscitation Cause Any Harm? *J Burn Care Res*. 2016. [Epub ahead of print].
- Medeiros DN, Ferranti JF, Delgado AF, et al. Colloids for the Initial Management of Severe Sepsis and Septic Shock in Pediatric Patients: A Systematic Review. *Pediatr Emerg Care*. 2015;31:e11-6.
- Boluyt N, Bollen CW, Bos AP, et al. Fluid resuscitation in neonatal and pediatric hypovolemic shock: a Dutch Pediatric Society evidence-based clinical practice guideline. *Intensive Care Med*. 2006;32:995-1003.
- Reid F, Lobo DN, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)*. 2003;104:17-24.
- Chua HR, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care*. 2012;27:138-45.
- Chopra A, Kumar V, Dutta A. Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. *Indian J Pediatr*. 2011;78:833-7.
- Schroth M, Plank C, Meissner U, et al. Hypertonic-hyperoncotic solutions improve cardiac function in children after open-heart surgery. *Pediatrics*. 2006;118:e76-84.
- Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243-51.
- Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247-56.
- Vincent JL, Russell JA, Jacob M, et al. Albumin administration in the acutely ill: what is new and where next? *Crit Care*. 2014;18:231.
- Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317:235-40.
- Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874-84.
- Finfer S, McEvoy S, Bellomo R, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med*. 2011;37:86-96.
- Roberts I, Blackhall K, Alderson P, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. 2011;11:CD001208.
- Lynch SK, Mullett MD, Graeber JE, et al. A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. *J Perinatol*. 2008;28:29-33.

48. Choo WP, Groeneveld AB, Driessen RH, et al. Normal saline to dilute parenteral drugs and to keep catheters open is a major and preventable source of hypernatremia acquired in the intensive care unit. *J Crit Care*. 2014;29:390-4.
49. McNab S. Intravenous maintenance fluid therapy in children. *J Paediatr Child Health*. 2016;52:137-40.
50. Guarnier J, Hochman J, Kurbatova E, et al. Study of outcomes associated with hyponatremia and hypernatremia in children. *Pediatr Dev Pathol*. 2011;14:117-23.
51. Darmon M, Pichon M, Schwebel C, et al. Influence of Early Dysnatraemia Correction on Survival of Critically Ill Patients. *Shock*. 2014;41:394-9.
52. Lang F. The Body Compartments and dynamics of water and electrolytes. In: Gregor RWU (Eds). *Comprehensive Human Physiology*, 2nd edition. Berlin Heidelberg: Springer-Verlag; 1996.
53. Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. *Adv Exp Med Biol*. 2013;788:103-8.
54. Williams CN, Belzer JS, Riva-Cambrin J, et al. The incidence of postoperative hyponatremia and associated neurological sequelae in children with intracranial neoplasms. *J Neurosurg Pediatr*. 2014;13:283-90.
55. Fajardo JE, Stafford EM, Bass JW, et al. Inappropriate antidiuretic hormone in children with viral meningitis. *Pediatr Neurol*. 1989;5:37-40.
56. Judd BA, Haycock GB, Dalton RN, et al. Antidiuretic hormone following surgery in children. *Acta Paediatr Scand*. 1990;79:461-6.
57. Lim YJ, Park EK, Koh HC, et al. Syndrome of inappropriate secretion of antidiuretic hormone as a leading cause of hyponatremia in children who underwent chemotherapy or stem cell transplantation. *Pediatr Blood Cancer*. 2010;54:734-7.
58. Patient Safety Alert 22. Reducing the risk of hyponatraemia when administering intravenous infusions to children. NHS National Patient Safety Agency. 2007.

Antibiotic Resistance: A Global Threat

Banani Poddar

INTRODUCTION

Infections have plagued man since the beginning of human existence. It was not until the spectacular discovery of penicillin by Alexander Fleming that man found an effective method of treating patients with infections. This turned out to be a turning point in medicine as innumerable lives were saved by antibiotics. Over the years, newer and better antibiotics have enabled medicine to progress such that more complex therapies and procedures are regularly performed. These include organ transplantation, placement of prosthesis, cancer chemotherapy, and complex surgeries. However, resistance to antibiotics has been growing at an alarming rate and threatens this progress in medicine.

WHAT IS ANTIBIOTIC RESISTANCE?

Antibiotic resistance is the ability of microbes to grow in the presence of a drug, which would normally be lethal to them or limit their growth.¹ In other words, microorganisms that are not inhibited by usually achievable systemic concentration of an antibiotic agent with normal dosage schedule are said to be resistant.

WHAT ARE THE EFFECTS OF ANTIBIOTIC RESISTANCE?

Infections that could normally be treated with antibiotics would not respond to antibiotics leading to the use of more powerful (and often more expensive) antibiotics, thus escalating cost of therapy and prolonging hospital stay. Further, in certain situations, infections may not respond to all available antibiotics, thus increasing mortality. Much of the progress in medicine depends on the use of effective antibiotics. This ranges from simple surgeries like cesarean section to complex therapies such as organ transplantation. None of these would be possible without effective antibiotics and the threat of return to the "preantibiotic era" is very real and calls for urgent action.

HISTORY OF ANTIBIOTIC RESISTANCE

Man and microbes have always been at war with each other. Any effective anti-infective therapy introduced by man is countered by the emergence of resistance, making the therapy ineffective over a few years of use. Sulfonamides were perhaps the first effective antibiotics and resistance to these developed in the late 1930s. Alexander Fleming, in his Nobel Prize acceptance speech in 1945, warned about resistance to penicillin and recognized some of the risk factors for development of resistance. He said "It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug, make them resistant".²

It is interesting to note that even before penicillin was widely used, in 1940, a bacterial penicillinase was discovered! This assumes great significance as recent investigations have revealed that several genes, which confer resistance, are found naturally in microbes.³

In the 1950s, genetically transmissible antibiotic resistance was identified in Japan. Since then, the literature about transfer of resistance by plasmids, integrons, and transposons has grown enormously. The practical implications of this genetic transfer have become obvious as the burden of antibiotic resistance is growing.

The timeline of introduction of antibiotics and development of resistance is shown in figure 1.

WHY DOES RESISTANCE OCCUR AND WHAT SUSTAINS IT?

Antibiotic resistance is either intrinsic (i.e., natural) or acquired. Some bacteria are intrinsically resistant to certain classes of antibiotics. However, in some, resistance is either acquired due to mutations. And in some instances, resistance

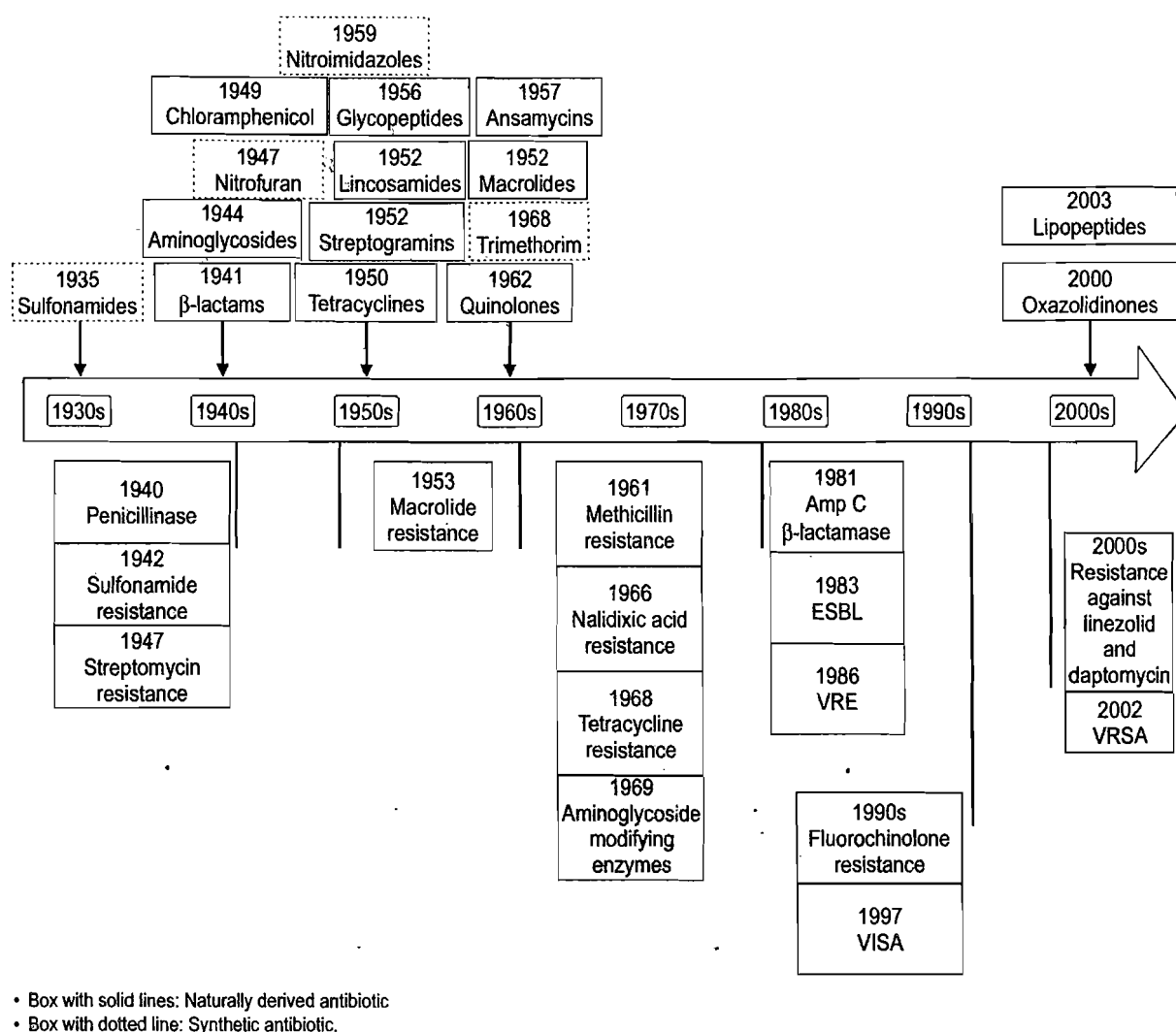


FIG. 1: Timeline of introduction of antibiotics and development of resistance

is conferred by genetic elements, which are transferred from one organism to the other.

Bacteria have to compete with each other for nutrition and other resources and hence they naturally produce substances, which can harm each other.⁴ These natural substances have been deployed by humans as antibiotics. Just as antibiotics exist in nature, these microbes also produce substances, which can nullify the effect of these antibiotics; in other words, mechanisms to resist the effects of antibiotics occur naturally in these microbes. The exact reason why substances with antibiotic properties are produced by microbes is not clear; perhaps bacteria use these as signaling molecules. Hence, there is a fine balance in the environment which keeps the microbial numbers in check. The introduction and large-scale use of antibiotics by humans has changed all this and tilted the balance in favor of antibiotic resistance. The following factors have enhanced antibiotic resistance:

- Excessive use of antibiotics:
 - Prescribed for wrong/flimsy indications: Since antibiotics are relatively harmless, these have been prescribed extensively, often for viral infections

or noninfectious causes. In developing countries, antibiotics are available over the counter and hence these are often overused

- Prescribed for inadequate or excessively long durations: When antibiotics are self-prescribed, often the dose and duration are inadequate. On the other hand, in critically ill patients or hospitalized sick patients, prolonged courses of antibiotics are prescribed
- Prescribed in an inadequate dose
- Multiple antibiotics prescribed, especially in hospitalized patients
- Spurious antibiotics: Generic antibiotics are often inadequately regulated and the quality and strength remain unchecked
- Extensive use of antibiotics in the poultry and meat industry
- Extensive use of antibiotics in agriculture and aquaculture.

The last two have resulted in the wide dissemination of antibiotics in the environment and humans are exposed to antibiotics in food, thus building an environment

conductive to antibiotic resistance. In addition to all the above, large quantities of antibiotics have been dumped in the environment without concerns regarding the long-term effects of this dumping.

Human-to-human transmission of resistant microbes occurs to a large extent in health care settings. In areas of high-antibiotic use, such as intensive care units, patients are heavily colonized with resistant bacteria and transmission of such infections, too, is highest in these settings as healthcare workers come in close contact with these patients. Human-to-human transmission also occurs in the community through environmental contamination (fecal-oral transmission). Animal-to-human transmission occurs either through environmental contamination (water, food, etc.) or through the food chain.

Figure 2 aptly depicts the contribution of various factors to antibiotic resistance.

GEOGRAPHICAL DISTRIBUTION OF ANTIBIOTIC RESISTANCE

Antibiotic resistance is a global problem and exists everywhere. However, there are geographical differences, and the burden is higher in developing countries.

Molton et al. in a recent review on the global spread of drug-resistant bacteria, bemoans the rapid spread of New Delhi metallo- β -lactamase-1 (NDM-1) across the globe thus "Since antibiotics were first used, each new introduced class has been followed by a global wave of emergent resistance, largely originating in Europe and North America where they were first used. Methicillin-resistant *Staphylococcus*

aureus spread from the United Kingdom and North America across Europe and then Asia over more than a decade. Vancomycin-resistant enterococci and *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* followed a similar path some 20 years later. Recently, however, metallo- β -lactamases have originated in Asia. New Delhi metallo- β -lactamase-1 was found in almost every continent within a year of its emergence in India. Metallo- β -lactamase enzymes are encoded on highly transmissible plasmids that spread rapidly between bacteria, rather than relying on clonal proliferation. Global air travel may have helped facilitate rapid dissemination".⁵

Excellent interactive graphs of the geographical distribution of antibiotic resistance are available at the link <http://resistancemap.cddep.org/resmap/resistance>.

MECHANISMS OF RESISTANCE

Antibiotic resistance is produced by one of the following mechanisms:

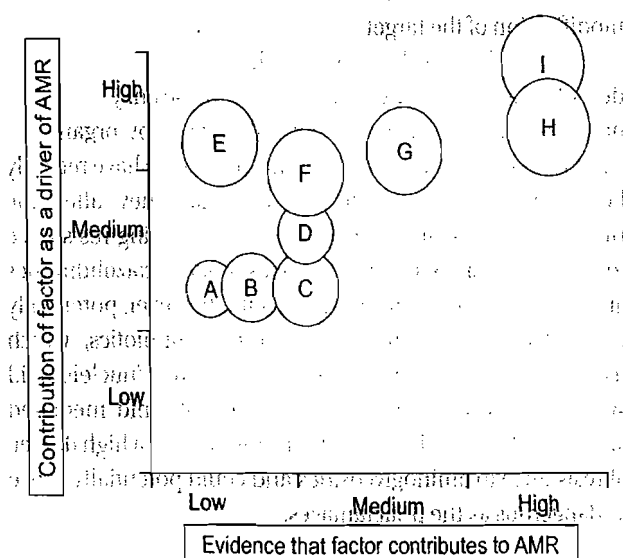
- Enzymes produced by bacteria, which lyse the antibiotic or alter its structure, e.g., β -lactamases
- Alteration of the target, e.g., resistance to fluoroquinolones
- Inability of the antibiotic to reach adequate concentration in the bacterial cell:
 - Inability of the antibiotic to reach the bacterial cell, e.g., altered porin channels
 - Efflux of the antibiotic from the bacterial cell.

In each of the above mechanisms, it can be deduced that the antibiotic is either unable to reach the target site of action or does so in an inadequate concentration and hence is unable to act on the bacteria. Figure 3 diagrammatically represents the mechanisms of action of antibiotics and how bacteria develop resistance to them.

A complete review on this topic is beyond the scope of this article; each of the mechanisms is briefly described and their implications in clinical antibiotic prescribing highlighted.

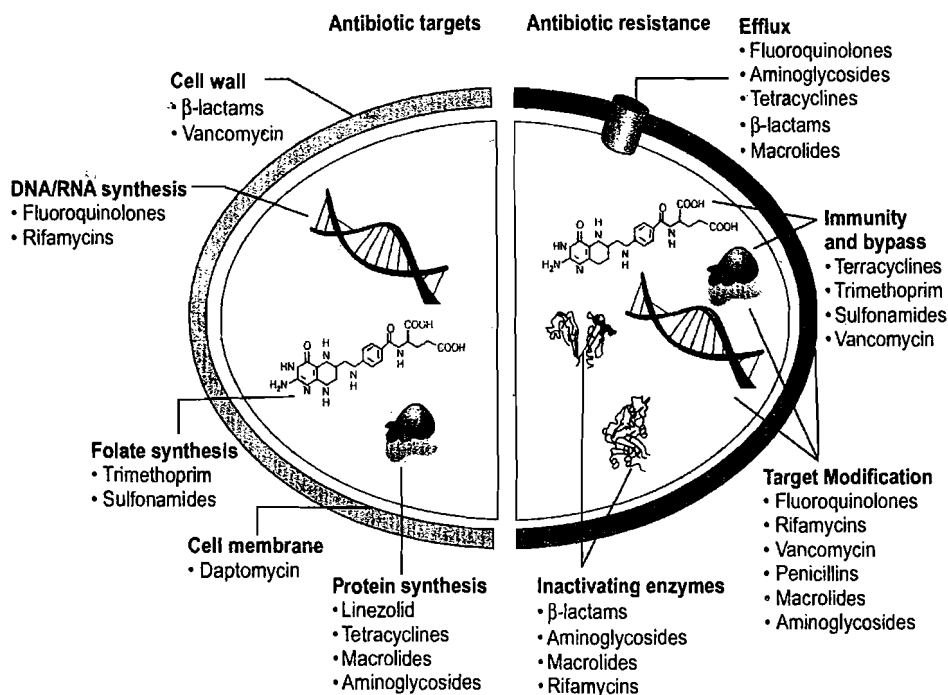
Beta-lactamases

Penicillinase, the forerunner of β -lactamases was discovered even before penicillin was widely used. Widespread use of β -lactam (BL) antibiotics has led to a large number of enzymes, which degrade these antibiotics and these are known as β -lactamases. They target the BL ring of these antibiotics and degrade penicillins, cephalosporins, carbapenems, and monobactams. Each effort by humans to counter mechanisms of resistance has met with more complex and broad-spectrum β -lactamases. Many of these are genetically determined and horizontal gene transfer ensures easy transmission of resistance. These are widely distributed internationally and are largely responsible for the important nosocomial infections. What is most worrisome is the fact that many of these are now responsible for community-acquired infections. Today, β -lactamases are



A, mass drug administration; B, travel; C, suboptimal vaccination; D, environmental contamination; E, suboptimal dosing; F, suboptimal rapid diagnostics; G, healthcare transmission; H, animal antimicrobial misuse; I, human antimicrobial misuse; AMR, antimicrobial resistance.

FIG. 2: Factors contributing to the development of antimicrobial resistance



DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

FIG. 3: Diagrammatic representation of the mechanisms of action of antibiotics and how bacteria develop resistance to them

the most important determinants of antibiotic resistance, especially in Gram-negative pathogens.

A classification of the β -lactamases, the antibiotic substrates on which they act and their inhibition by clavulanic acid or other β -lactamase inhibitors (BLI), is available.⁶ The evolution and a simplistic classification of β -lactamases are as follows:

- Early β -lactamases only hydrolyze penicillins
- Broad-spectrum β -lactamases hydrolyze modified penicillins (e.g., aminopenicillins) and the narrow-spectrum cephalosporins. These are easily inhibited by clavulanic acid or other BLI
- Extended spectrum β -lactamases (ESBL) hydrolyze third and fourth generation cephalosporins and monobactams, but are inhibited by BLI
- AmpC β -lactamases hydrolyze cephamycins in addition to cephalosporins and are not inhibited by BLI
- Carbapenemases hydrolyze carbapenems, as the name suggests, and are not inhibited by BLI. The detection of NDM in 2008 and its spread across the globe has raised alarm bells regarding the rapid spread of antibiotic resistance.

It is obvious that the impact of β -lactamases in clinical practice is far from trivial. Knowledge regarding the strains of organisms prevalent in each location and their antibiotic susceptibility is important for starting empirical therapy in patients. The important β -lactamases, their characteristics, and potential treatment options is as seen in table 1.⁷ While it is generally accepted that carbapenems are the drugs of choice in serious Gram-negative infections (if ESBL is suspected),

recent literature is challenging this concept. A combination of BL-BLI may be considered in several situations to prevent the widespread emergence of carbapenem resistance.^{7,8}

Alteration of the Target

Antibiotic resistance to aminoglycosides, macrolides, fluoroquinolones, and vancomycin is commonly due to modification of the target.

One of the novel enzymes, which have recently been described are the methyl transferases.³ These enzymes occur naturally and are used as a natural defense by organisms, which produce aminoglycosides; however, they have recently been described in pathogenic bacteria. They alter the ribosomal ribonucleic acid (rRNA), thus causing resistance to aminoglycosides, phenicols, lincosamides, oxazolidinones and streptogramin A. Resistance could, however, potentially be conferred to macrolides and other antibiotics, which use this pathway to disrupt bacterial protein/nucleic acid synthesis. These methyltransferases are plasmid mediated and are widespread in distribution. They confer a high degree of resistance to aminoglycosides and could potentially prove as dangerous as the β -lactamases.

Inability of the Drug to Achieve Adequate Intracellular Concentration

Drugs enter the bacterial cell through channels known as "porin" channels. Several bacteria develop resistance to antibiotics by altering these channels. Further, efflux pumps

TABLE 1 Characteristics of important β -lactamases and potential treatment options

Enzymes	Activity	Ambler class	Active site residue	Resistance gene location	β -lactams inactivated	Examples of current treatment options
ESBL	ESBL	A	Serine	Plasmid	First-to-fourth generation Cephalosporins, Aztreonam, older BLBLIs	<ul style="list-style-type: none"> Carbapenems, possibly BLBLIs, e.g., piperacillin-tazobactam in low inoculum, nonsevere infections, such as cystitis
AmpC	Carbapenemases	C	Serine	Chromosomal (inherent in some genera, such as <i>Enterobacter</i> , <i>Serratia</i> <i>Citrobacter</i>), occasionally plasmid	First-to-third generation Cephalosporins, older BLBLIs, Carbapenems	<ul style="list-style-type: none"> Cefepime (in select patients, such as those needing only a short course of therapy, low-inoculum, nonsevere infections) Carbapenems
KPC	Carbapenemases	A	Serine	–	First-to-fourth generation Cephalosporins, Aztreonam, older BLBLIs, Carbapenems	<ul style="list-style-type: none"> More data needed Polymyxin, Tigecycline, and Aminoglycosides combination treatment, consider including a Carbapenem Cystitis: Fosfomycin (oral) Nitrofurantoin
NDM	Carbapenemases	B	Zinc	–	First-to-fourth generation Cephalosporins, older BLBLIs, Carbapenems	<ul style="list-style-type: none"> More data needed Polymyxins, Tigecycline, and Aminoglycosides Aztreonam combination treatment, consider including a Carbapenem Cystitis: Fosfomycin (oral) Nitrofurantoin
OXA-48 group	Carbapenemases	D	Serine	–	First-to-fourth generation Cephalosporins, Carbapenems. Variable or diminished hydrolysis of third or fourth generation Cephalosporins possible	<ul style="list-style-type: none"> More data needed Polymyxins, Tigecycline, and Aminoglycosides Consider a β-lactam in combination with the above, choice dependent susceptibility testing Third-generation Cephalosporin (e.g., ceftazidime) may retain activity and may be preferable to Carbapenems

Note: Older BLBLIs are amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam and ticarcillin-clavulanate. New BLBLIs such as Ceftazidime-avibactam and Aztreonam-avibactam have activity against ESBLs, AmpCs, and KPCs. Aztreonam-avibactam has activity against NDMs.

BLBLI, β -lactam β -lactamase inhibitor; ESBL, extended spectrum β -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- β -lactamase.

are activated or incorporated, which actively pump out the antibiotics. Resistance to fluoroquinolones, macrolides, and aminoglycosides often occur due to these mechanisms.

"Inoculum" Effect

When a large number of bacteria infect the patient, this is said to be a large "inoculum". In such a scenario, antibiotics which under-laboratory conditions are effective against the cultured organisms may not be effective clinically. The high density of bacteria produces substances, which render the antibiotic ineffective (e.g., hydrolyzing enzymes).⁹

Role of Biofilms in Antibiotic Resistance

Biofilms are a collection of bacteria, often of more than one species, enmeshed in an extracellular matrix.^{9,10} Various signaling molecules and substances for "quorum sensing" are deployed in these biofilms. Antibiotics are unable to penetrate into this biofilm; thus a mechanism to escape their action. Any foreign substance introduced into the body (endotracheal tube, central venous catheter, urinary catheter, medical implant, etc.) acquires a biofilm over time. Bacteria, which are rapidly multiplying are released from time to time from these biofilms and when tested for antibiotic susceptibility, they are found to be susceptible. However,

the biofilm harbors slow growing “persisters”, which are less susceptible to antibiotics. Immune cells, also, are often unable to reach the biofilms to eradicate bacteria. The importance of biofilms in persistence of infection and antibiotic resistance is increasingly being recognized.

GENETICS OF BACTERIAL RESISTANCE

Most of the medically important antibiotic resistance is acquired either due to mutations or mobile-genetic elements. While resistance due to mutations is slow to develop and depends on vertical transmission (from one generation to the next), mobile-genetic elements are transmitted horizontally. Not only are they transmitted to other bacteria of the same species, they can easily be transmitted to bacteria of other species.

Plasmids

These are extrachromosomal genetic materials, which multiply independent of bacterial deoxyribonucleic acid (DNA) and freely in the bacterial cytoplasm. They contain resistance genes (or r-genes) and these are easily exchanged/ transferred between plasmids or between plasmids and chromosomes.

Plasmids have emerged as one of the most important vehicles of antibiotic resistance.

Transposons

These are sequences of DNA, which move around the genome of a bacterial cell. Plasmids integrate a transposon and pass it on to other plasmids or to the bacterial chromosome. Hence, they are aptly referred to as “jumping genes”.

Integrans

Integrans are large DNA sequences, which are often packed with multiple gene cassettes. Each gene cassette contains an r-gene attached to a small recognition site. Apart from resistance, these integrans encode several bacterial functions such as virulence. Integrans are not mobile themselves; however, they are distributed widely in the environment and are crucial for the transfer of r-genes. They are considered to be important for resistance in Gram-negative bacteria; their rôle in Gram-positive bacteria is not yet clear.

Genetic material is transferred between bacteria by one of three mechanisms: (i) conjugation, (ii) transduction, and (iii) transformation.

IMPORTANT NOSOCOMIAL PATHOGENS IN CRITICALLY ILL PATIENTS AND THEIR MANAGEMENT

Several organisms have emerged as “superbugs”, especially in patients within the confines of the intensive care unit.³ The

ESKAPE pathogens, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species are responsible for a large majority of nosocomial infections. They are notoriously difficult to treat in view of their resistance profiles and are responsible for increased morbidity and mortality of hospitalized patients.^{8,11}

Gram-negative pathogens are responsible for the majority of infections in developing countries such as India. These organisms have multiple mechanisms of antibiotic resistance and each organism may have genes encoding for resistance to multiple groups of antibiotics. *Escherichia coli* (or *E. coli*) and *Klebsiella* are the most common organisms and produce ESBL. AmpC, porin channel loss, and efflux pumps are also prevalent, but they pale in comparison to the impact of ESBLs. *Klebsiella* is further armored with several carbapenemases such as KPC and NDM, all of which are plasmid mediated. *Acinetobacter*, *Pseudomonas*, and *Enterobacter* are very difficult to eradicate and thrive on hospital environments. These bacteria have thick outer membranes and are generally less permeable to several antibiotics. In addition, they are often equipped with efflux pumps. These latter bacteria too can acquire plasmids and thus demonstrate high-level antibiotic resistance.

Suggestions regarding their treatment are shown in table 1. Treatment needs to be individualized considering susceptibility results, pharmacodynamics and pharmacokinetics, site of infection, and patient factors (risk profile, allergies, and organ failures). The polymyxins are toxic drugs, which are being used again today due to the emergence of resistance; however, *Serratia*, *Proteus*, and *Providencia* are inherently resistant to these. Tigecycline, a newer antibiotic has no activity against *Pseudomonas*, *Proteus*, and *Providencia*. Moreover, it is bacteriostatic and achieves poor serum and urine levels. Hence, it should not be used as monotherapy in bloodstream infections or in urinary tract infections.

Gram-positive organisms, on the other hand, have simpler peptidoglycan-rich cell wall and hence penetration of antibiotics is not an issue. *Enterococcus* is a fastidious organism and is inherently resistant to certain antibiotics such as penicillin and aminoglycosides. However, recently, *Enterococcus faecium* is gaining importance, especially in complicated intra-abdominal infections. Resistance to BL antibiotics and vancomycin due to acquired mechanisms (β -lactamases and Van A mutations) have made *Enterococci* an important nosocomial pathogen, especially in bloodstream infections and endocarditis.¹² *Staphylococcus aureus* is a virulent organism, which causes necrotizing infections (pneumonia, soft-tissue infections, osteomyelitis, etc.) and resistance to penicillin was first described in this organism. Methicillin, one of the first modifications of penicillin, was effective until the 1960s. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are now among the most dangerous infections reported from the developed countries. Initially

seen only in hospitals, now they are routinely reported from the community as well. In India, resistance to methicillin is widely prevalent in hospital settings; recently community-acquired infections with MRSA have been reported.

WHY IS INDIA AT THE TOP OF ANTIBIOTIC RESISTANCE?

India is peculiarly poised as on one hand it has a very high burden of infectious diseases and there is a need to make antibiotics more affordable and accessible. On the other hand, antibiotics are easily available and there is neither a check on the access nor on the quality of antibiotics and hence they are abused.^{4,13} The onus of resistance in India lies not only with the medical fraternity, but also with the patient and with the lack of commitment from the government. Patients often self-administer antibiotics for viral infections, respiratory and gastrointestinal being the most common. Antibiotics prescribed for actual infections are very often taken for durations shorter than recommended and/or in lower doses. Similarly, at the level of the physicians, all febrile patients are prescribed antibiotics, irrespective of their need for the same. Lack of proper and timely diagnostics further compounds the dilemma faced by clinicians. Polypharmacy, especially in hospitalized patients is common. The presence of a large number of generics of questionable quality and poor consideration for infection control policies abets antibiotic resistance. Policy makers have little time or inclination to control this looming threat; lack of commitment affects health and infectious diseases, in particular, at all levels—poor environmental sanitation, lack of provision for safe drinking water, lack of regulation of available antibiotics by the drug controller, inadequate vaccination coverage, and inadequate infection control policies. Unregulated use of antibiotics in animal industry, agriculture, and aquaculture also adds to the problem.

WHAT NEEDS TO BE DONE TO CONTROL ANTIBIOTIC RESISTANCE?

Fortunately, a lot can be done and needs to be done. These could be divided as action required from:

- Clinicians:
 - Judicious use of current antibiotics
 - Antimicrobial stewardship
- Microbiologists:
 - Rapid diagnostics to aid the diagnosis of infections with timely antimicrobial sensitivities
- Hospital administrators:
 - Ensure implementation of hospital infection control policy including proper waste management and antimicrobial stewardship
- Pharmacologists and drug manufacturers:
 - Ensure proper quality of drugs that are marketed

- Promote research on new drugs to combat infections
- Policy makers:
 - Environmental sanitation
 - Clean drinking water
 - Vaccination
 - Regulation of drugs available in the market
 - National policy on antimicrobials
 - Encourage research in infectious diseases
- One health approach:
 - Integrating the health needs of humans and animals and stopping or minimizing the use of antibiotics in agriculture and aquaculture.

Judicious Use of Antibiotics

The life of the current antibiotics can be extended, if every clinician follows the principles of antimicrobial stewardship. These include:

- The right patient
- The right drug
- The right dose
- The right duration
- Deescalation.

Right Patient

A proper indication to start a particular drug is based on locally prevalent organisms and risk factors. Risk stratification of patients prevents unnecessary antibiotics in low-risk patients and appropriate therapy in high-risk patients. However, it is imperative on the clinician to send the appropriate laboratory workup (including cultures) to be able to quickly identify the responsible organism and tailor the antibiotic regime to the reports.

Right Drug

Clinicians can choose the right drug for patients only if the prevalent microbiology is known. Inability to start appropriate antibiotics leads to adverse outcomes.

Right Dose and Duration

As discussed previously under dosing abets antibiotic resistance, depending on the severity of illness, the highest possible dose of the drug required for that particular infection should be given. If facilities for drug level monitoring are available, adequate levels should be achieved and maintained. Further, the drug should be continued for an adequate duration. Prolonged duration of antibiotics also promotes the selection of resistant organisms; hence, these should be avoided.

Simultaneous with the above two, a search for the source of infection should include appropriate radiological imaging.

Source control (e.g., drainage of infected collections) is equally important as antibiotics often do not penetrate infected collections.

Deescalation

This is the step where most clinicians falter. Once cultures are available, antibiotics should be tailored to the narrowest spectrum possible. If cultures are negative, antibiotics should be considered to be stopped. Noninfectious causes should be sought, if cultures are negative. If the patient's condition has improved significantly, parenteral therapy should be switched to oral therapy.

Antimicrobial Stewardship Program

Ideally, every hospital needs an antibiotic stewardship program, which ensures the judicious use of antibiotics. Certain drugs should be considered "reserved" and should require prior authorization or justification.

Nathwani et al. described antimicrobial stewardship as an "interprofessional effort across the continuum of care. It involves timely and optimal selection, and dose and duration of an antibiotic for the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on resistance and other ecological adverse effects".¹⁴

Centers for Disease Control has defined the core elements of an antimicrobial stewardship program as below:¹⁵

- **Leadership commitment:** Dedicating necessary human, financial, and information technology resources
- **Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective
- **Drug expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use
- **Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 h)
- **Tracking:** Monitoring antibiotic prescribing and resistance patterns
- **Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses, and relevant staff
- **Education:** Educating clinicians about resistance and optimal prescribing.

Outpatient Parenteral Antibiotic Therapy

Another important intervention to prevent colonization with resistant pathogens is to discharge a patient early and, if continued, parenteral antibiotic therapy is required, this can be continued on an outpatient basis.

Role of the Microbiology Laboratory

Lack of appropriate diagnostics drives antibiotic resistance.^{13,16,17} If a reliable method of diagnosis, which is accurate and has a rapid turnaround time is available, clinicians would prefer to use it before empirically prescribing antibiotics. Unfortunately, most methods of diagnosis are expensive (as they require an expensive laboratory set up), time consuming (take up to several days for cultures) and are yet not 100% sensitive and/or specific.

Biomarkers such as C-reactive protein and procalcitonin can guide antibiotic therapy to some extent but cannot be used as the gold standard. However, incorporating such biomarkers in the treatment algorithms decreases the duration of antibiotic exposure. Research for more reliable markers is ongoing.

The turnaround time for cultures has been progressively decreasing. Recent automated systems need 4–6 hours to have a reliable report (VITEK-2 system). However, sometimes the appropriate sample cannot be taken in time and hence cultures may be negative. Molecular diagnostics such as polymerase chain reaction, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and next generation sequencing have revolutionized diagnostics and have improved accuracy and time to reporting. Needless to say, such laboratory diagnostics need costly laboratory infrastructure and may not be feasible in low- and middle-income countries.

Reliable but cheap tests, which require minimal infrastructure, with a focus on chromogenic tests are required in low- and middle-income countries.

ALTERNATIVES TO ANTIBIOTICS: WHAT THE FUTURE HOLDS

Several alternatives to antibiotics are in the pipeline and seem to be promising. However, none of them have reached the stage of being marketed and would require time to be accepted as standard therapy.¹⁸ Some of the approaches are detailed in table 2.

Quorum Sensing

Bacteria have unique mechanisms of communication and signaling with the use of certain chemical substances. These act as autoinducers and allow the bacterial population to coordinate gene expression for virulence, conjugation, apoptosis, mobility, and resistance. Substances, which inhibit these signaling molecules could render whole colonies of bacteria ineffective and thus promote their destruction. Some such substances have been found in natural substances, e.g., garlic extracts. Some substances have been synthesized too. Animal models of inhibitors of quorum sensing have shown promising results.

TABLE 2 Alternative approaches to antibiotics

Newer therapy	Mechanism of action/therapeutic potential
Antibodies	Antibodies that either bind to the organism or its virulence factor or its toxin
Phage therapy	Either wild type bacteriophages, which infect bacteria and destroy them or engineered phages which can perform certain specific antibacterial action
Lysins	Lytic enzymes (as found in saliva or mucus), which have a direct lytic action due to their action on cell wall
Inhibitors of quorum sensing	See details in text
Agents to target type IIa topoisomerases	Inhibit bacterial replication
Antimicrobial peptides or lipopeptides	These inhibit cell membrane formation in bacteria and are effective in a Gram-positive and Gram-negative bacteria. Potential for resistance considered very low as bacteria will have to change their entire cell membrane
Efflux pump inhibitors	Inhibit efflux pumps

CONCLUSION

It is obvious that resistance to antibiotics is fast expanding globally and is a threat to medicine and its progress. Simple diseases and procedures could become life threatening, if antibiotic resistance is not contained. The responsibility to judiciously use this precious resource lies with the physician; however, action is required from almost every walk of society. The rampant use of antibiotics in animal industry (or rather and food industry) and in agriculture should urgently be checked. Implementation of antibiotic stewardship program at every healthcare facility and on the larger scene, nationally, is an important step to improve the life of current antibiotics. While newer antibiotics do not seem to be on the horizon, alternative strategies to treat infections are being tested and could change this gloomy picture.

REFERENCES

1. National Institute of Allergy and Infectious diseases, National Institutes of Health. Understanding antibiotic (drug) resistance. [online] Available from: <https://www.niaid.nih.gov/topics/antibioticresistance/understanding/Pages/definitions.aspx>. [Accessed November, 2016].
2. Alexander Fleming. (1945). Penicillin. Nobel lecture, December 11, 1945. [online] Available from: www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf. [Accessed November, 2016].
3. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev.* 2010;74:417-33.
4. Holmes AH, Moore LSP, Sundsfjord A, et al. Antimicrobials: access and sustainable effectiveness 2. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet.* 2016;387:176-87.
5. Molton JS, Tambyah PA, Ang BS, et al. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. *Clin Infect Dis.* 2013;56:1310-8.
6. Jacoby GA, Munoz-Price LS. The new β -lactamases. *N Engl J Med.* 2005;352:380-91.
7. Vasoo S, Barreto JN, Tosh PK. Emerging issues in Gram-negative bacterial resistance: an update for the practicing clinician. *Mayo Clin Proc.* 2015; 90:395-403.
8. Harris PNA, Tambyah PA, Paterson DL. β -lactam and β -lactamase inhibitor combinations in the treatment of extended-spectrum β -lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options? *Lancet Infect Dis.* 2015;15:475-85.
9. Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae. Mechanisms and clinical implications. *BMJ.* 2015;351:h6420.
10. Gupta P, Sarkar S, Das B, Bhattacharjee S, et al. Biofilm, pathogenesis and prevention—a journey to break the wall: a review. *Arch Microbiol.* 2016;198:1-15.
11. Santajit S, Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *Biomed Res Int.* 2016;2016:2475067.
12. Hollenbeck BL, Rice LB. Intrinsic and acquired resistance mechanisms in enterococci. *Virulence.* 2012;3:421-569.
13. Mendelson M, Røttingen JA, Gopinathan U, et al. Antimicrobials: access and sustainable effectiveness 3. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet.* 2016;387:188-98.
14. Nathwani D. Antimicrobial stewardship. In: Mayhall GC (Eds). *Hospital epidemiology and infection Control.* 4th ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.
15. Centers for Disease Control and Prevention. (2015) Core elements of hospital antibiotic stewardship programs. [online] Available from: <http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>. [Accessed November, 2016].
16. Callendo AM, Gilbert DN, Ginocchio CG, et al. Better tests, better care: Improved diagnostics for infectious diseases. *Clin Infect Dis.* 2013;57:S139-70.
17. Lakshminarayan R, Duse A, Wattal C, et al. Antimicrobial resistance—the need for global solutions. *Lancet Infect Dis.* 2013;13:1057-98.
18. Czaplewski L, Bax R, Clorie M, et al. Alternatives to antibiotics—a pipeline portfolio review. *Lancet Infect Dis.* 2016;16:239-51.

Management of Pediatric Acute Respiratory Distress Syndrome

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of pulmonary inflammation following direct or indirect pulmonary insult characterized by hypoxemia and respiratory failure. Children have varying incidence of acute lung injury (ALI)/ARDS from 2.2 to 16 per 100,000 pediatric populations associated with high morbidity, mortality, and financial burden. The traditional diagnostic criteria include acute onset, severe arterial hypoxemia resistant to oxygen therapy alone [partial arterial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio ≤ 200 for ARDS and ≤ 300 for ALI], diffuse pulmonary inflammation (bilateral infiltrates on chest radiograph), and no evidence of left atrial hypertension on echocardiography. But recently the diagnostic criteria of pediatric ARDS (PARDS) have been revised by the consensus recommendations from the Pediatric ALI Consensus Conference (PALICC)¹⁻⁵ (Table 1).

MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME^{6,7}

Managing a PARDS, though stands on the same principles as in adults, but somehow different from adults in a few aspects and the management is broadly divided into three broad headings:

1. Control of causative factors
2. Respiratory support
3. Nonrespiratory support.

A dedicated team of pediatric intensivists, nursing staff with other supportive staff in a well-equipped tertiary level-3 PICU is required to manage a child with PARDS.

General guidelines have been summarized below in the box (Box 1). The key issues in management involve treating the cause or the primary insult, to provide adequate oxygenation and ventilation while minimizing ventilator-induced lung injury (VILI) to improve tissue perfusion by providing adequate hemodynamic support and taking care of the fluid, electrolyte and nutrition.

Control of Causative Factors

Trigger source identification and source control are of paramount importance in management of ARDS. Sepsis being a common trigger for ALI/ARDS, early, optimum, and appropriate antibiotic therapy is recommended in cases of pneumonia and septic shock.

Clinical conditions associated with development of ALI/ARDS are depicted in table 2.

Respiratory Support

There is wide range of variability on the degree of respiratory support required in ARDS. Depending on the severity it may range from supplemental oxygen to assisted ventilatory support. Assisted ventilator support may be complicated by volutrauma due to alveolar overdistension of the normally aerated lung and atelectrauma due to repeated opening and closing of the alveoli, both of these complications lead to VILI and oxygen toxicity due to requirement of high-inspired concentration of oxygen is also a complication of assisted ventilation. The goal of ventilating patients with ALI/ARDS is to maintain adequate gas exchange with minimal VILI. Mechanical ventilator support can be both noninvasive or invasive.

Noninvasive Ventilation

In ARDS-noninvasive ventilation (NIV) is an excellent option in pediatric age group in wide variety of conditions. Few studies also have proved the usefulness of NIV in mild and moderate ARDS. It decreases the rates of intubation as well as the chances of ventilator-associated pneumonia (VAP). An isolated nasal mask or a full face mask both can be used in children depending upon the situation and tolerance. But a recent Cochrane Collaboration review concluded that there is a lack of well-designed and controlled experiments of noninvasive positive-pressure ventilation in children with acute hypoxemic respiratory failure. Only one small before-

TABLE 1 Pediatric acute respiratory distress syndrome definition

Age	Exclude patients with peri-natal related lung disease				
Timing	Within 7 days of known clinical insult				
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload				
Chest imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease				
Oxygenation	Noninvasive mechanical ventilation		Invasive mechanical ventilation		
	PARDS (no severity stratification)		Mild	Moderate	Severe
	Full face-mask bilevel ventilation or CPAP ≥ 5 cmH ₂ O ²		4 \leq OI \leq 8	8 \leq OI \leq 16	OI \geq 16
	PF ratio \leq 300 SF ratio \leq 264 ¹		5 \leq OSI \leq 7.5 ¹	7.5 \leq OSI \leq 12.3 ¹	OSI \geq 12.3 ¹
Special populations					
Cyanotic heart disease	Standard criteria above for age, timing, origin of edema, and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease ³				
Chronic lung disease	Standard criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above ³				
Left ventricular dysfunction	Standard criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction				

Note: (A) Use partial arterial pressure of oxygen (PaO₂)-based metric when available. If PaO₂ not available, mean fraction of inspired oxygen (FiO₂) to maintain peripheral capillary oxygen saturation (SpO₂) $\leq 97\%$ to calculate oxygen saturation index (OSI) or oxygen saturation/FiO₂ ratio. (B) For nonintubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation. (C) Acute respiratory distress syndrome severity groups stratified by oxygenation index (OI) or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease.

$\text{OI} = (\text{FiO}_2 \times \text{mean airway pressure} \times 100) / \text{PaO}_2$

$\text{OSI} = (\text{FiO}_2 \times \text{mean airway pressure} \times 100) / \text{SpO}_2$

OI, oxygenation index; OSI = oxygen saturation index.

Box 1: Management of acute respiratory distress syndrome

- Control of causative factors, especially medical or surgical therapy for infections
- **Respiratory support:**
 - Noninvasive ventilation (NIV)—applicable in mild or early ARDS through either a nasal or a full face mask
 - Conventional invasive mechanical ventilation—the strategies are:
 - *Permissive hypoxia*—to prevent the lungs from oxygen induced-injury, to keep the SpO₂ between 88 and 92 and pO₂ between 60 and 80 mmHg
 - *Permissive hypercapnia*—gentle low-pressure/low-volume ventilation and to accept a higher pCO₂ level as long as the pH is >7.2
 - *Low-tidal volume (Vt) ventilation*—to keep the Vt as low as 6–8 mL/kg
 - *PEEP titration*—to titrate the PEEP and keep it above the lower inflection point and to bring down the FiO₂ by 60%
 - *Adequate inspiratory time*
 - *Judicious application of recruitment maneuvers*
 - *Prone positioning*—in refractory hypoxemia
 - *Advanced ventilation:*
 - *High-frequency oscillatory ventilation (HFOV)*—early HFOV in selected cases vs. rescue HFOV in refractory cases
 - *ECMO (extracorporeal membrane oxygenation)*—the last option in refractory cases
- **Nonrespiratory support:**
 - Fluid electrolytes
 - Nutrition
 - Analgesia sedation
 - Judicious transfusion of blood products
 - Hemodynamic support
 - Other supportive therapies
- **Controversial therapies:**
 - Steroid
 - Inhaled NO
 - Surfactants
 - Prostacyclins

ARDS, acute respiratory distress syndrome; SpO₂, peripheral capillary oxygen saturation; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; NO, nitric oxide; PEEP, positive end-expiratory pressure

TABLE 2 Causes of acute respiratory distress syndrome

Direct injury	Indirect injury
Common: <ul style="list-style-type: none"> • Pneumonia • Aspiration pneumonia Rare: <ul style="list-style-type: none"> • Inhalational injury • Drowning and near drowning • Pulmonary contusion • Reperfusion injury • High altitude • Strangulation 	Common: <ul style="list-style-type: none"> • Sepsis and septic shock • Severe trauma • Multiple blood product transfusion • Transfusion-associated lung injury Rare: <ul style="list-style-type: none"> • Acute pancreatitis • Burn • Disseminated intravascular coagulation • Head injury • Drug overdose • Cardiopulmonary bypass

DIC, disseminated intravascular coagulation

after study in bronchiolitis and a very small randomized trial in acute hypoxemic respiratory failure have been published.⁸⁻¹¹

Conventional Invasive Mechanical Ventilation

Endotracheal intubation is needed for invasive ventilation. Contrary to the popular beliefs, cuffed endotracheal tubes can be used safely for all-age groups to ensure adequate positive end expiratory pressure delivery. Low pressure high volume cuffed (MICRO-CUFF) endotracheal tubes (ET) are preferred over the conventional cuffed ET tubes in pediatrics. Conventional invasive mechanical ventilation is associated with VILI. Over the decades, researchers have worked in this issue how to reduce the chances of VILI in a mechanically ventilated patient. These are the following strategies that are followed when ventilating a PARDS to allow a good gas exchange by reducing the chances of VILI.

Permissive Hypoxia

Ventilator management protocol for adults published by the National Institutes of Health ARDS Clinical Trials Network (ARDSNet) recommended PaO_2 target is 55–80 mmHg [peripheral capillary oxygen saturation (SpO_2) target 88–95%]. For children with ALI/ARDS, PaO_2 of 60–80 mmHg is usually considered safe as per expert opinion, but there are no studies supporting the safety of this target. High FiO_2 should be avoided to minimize the risk of direct cellular toxicity, to avoid reabsorption atelectasis, free-radical injury to lungs and systemic toxicity as well. Even though there is no clinical evidence to suggest a threshold value, most of the pediatric intensivists decrease FiO_2 below 0.6 as soon as possible and to target SpO_2 as low as 88–92%, but the effect of tolerating lower levels of oxygenation for prolonged periods on the developing brain is unknown; long-term follow-up studies in pediatric ALI/ARDS that evaluate neurologic function have not been performed. The recent PALICC recommendation concluded

that for mild PARDS with positive end-expiratory pressure (PEEP) <10 cmH_2O , SpO_2 should generally be maintained at 92–97%. They recommend that after optimizing PEEP, lower SpO_2 levels (in the range of 88–92%) should be considered for those with PARDS with PEEP at least 10 cmH_2O . They also recommend that when SpO_2 is $<92\%$, monitoring of central venous saturation and markers of oxygen delivery is needed.

Permissive Hypercapnia

Permissive hypercapnia during mechanical ventilation has led to significant decrease in ARDS mortality. Low-tidal volume ventilation with permissive hypercapnia is a lung-protective ventilation strategy to prevent mechanotrauma. In this strategy we allow the partial pressure of carbon dioxide (pCO_2) to be high as long as pH is >7.2 . No active measure in ventilation to decrease the pCO_2 is done unless the pH is <7.2 unless we want to neuroprotect the kid. There are also some theoretical concepts of downregulation of inflammatory cell activity and reduction of oxidant stress by inhibiting xanthine oxidase by keeping a relatively high pCO_2 .

Low-tidal Volume Ventilation¹²⁻¹⁶

The concept of low-tidal volume (6–8 mL/kg) avoiding the conventional 10–12 mL/kg for ventilation is another lung-protective ventilation strategy. It is well accepted in adults as well as in pediatrics over the last decade. The aim of this approach is to minimize VILI. Low-tidal volume with permissive hypercapnia prevents the lung from barotrauma as well as volutrauma by preventing repetitive overstretching of the damaged lung. Pediatric ALI Consensus Conference recommend using patient-specific tidal volumes according to disease severity. As per these recommendations, patients with preserved lung compliance should be ventilated with tidal volume closer to the physiological range (5–8 mL/kg ideal body weight), whereas patients with poor lung compliance should be ventilated with lower tidal volumes of 3–6 mL/kg predicted body. These guidelines also recommend to aim for an inspiratory plateau pressure limit of 28 cmH_2O , and slightly higher plateau pressures (29–32 cmH_2O) for patients with reduced chest wall compliance (chest wall edema) particularly in the absence of transpulmonary pressure measurements.

Positive End-expiratory Pressure Titration

It is an integral part of “open lung strategy” in ARDS ventilation. It improves oxygenation by providing movement of fluid from the alveolar to interstitial space, recruitment of small airways, and collapsed alveoli and an increase in functional residual capacity. In the open lung ventilation strategy, it is recommended to keep the PEEP above the lower inflection point as most of the modern pediatric ventilators are equipped with pulmonary graphics, but in the absence of static pressure-volume (PV) curve measurement it is practiced to keep PEEP between 8 cmH_2O and 20 cmH_2O . It should be progressively

increased by 2–3 cmH₂O increments to maintain saturation between 90 and 95% with FiO₂ <60%. The definition of optimum PEEP is still enigmatic, but the PEEP which can maintain SpO₂ around 90% with a FiO₂ of <60% and delivers a best tidal volume is the optimum PEEP. Excessive PEEP with chest X-ray evidence of overdistension of the lungs must be avoided. High PEEP may cause hypotension and hemodynamic instability and that should be taken care of. The PALICC stated that PEEP levels >15 cmH₂O may be needed for severe PARDS, although attention should be paid to limiting the plateau pressure.

Adequate Inspiratory Time

No clinical studies have specifically addressed inspiratory time. The I:E ratio may be increased to 1:1 or 2:1 (inverse ratio ventilation) to improve oxygenation. The utility of inverse ratio ventilation in PARDS has yet not been substantiated.

Application of Recruitment Maneuver

There are no randomized studies to indicate whether recruitment maneuvers like use of sigh, continuous positive airway pressure, or bilevel positive airway pressure influence outcome in children. This is practically a gray zone in pediatric ventilation without any clear recommendations and guidelines. Most of the pediatric intensivists practice recruitment maneuver in child with ARDS who desaturates either due to worsening lung condition or after disconnection of circuit for suctioning. This can be achieved by a manual inspiratory hold for 20–30 seconds or keeping the very high pressure around 40 for few seconds. One should carefully observe the child during the maneuver as there are chances of development of hemodynamic compromise as well as air leak during and after the maneuvers. It is also important to be sure that there is no air-leak before starting the maneuver. The PALICC recommended careful recruitment maneuvers in the attempt to improve severe oxygenation failure by slow incremental and decremental PEEP steps. Sustained inflation maneuvers cannot be recommended due to lack of available data.

*Prone Positioning*¹⁷

Prone ventilation has improved the oxygenation significantly and the recent publication in adults (PROSEVA study) has shown that prone positioning can improve the rate of survival as well as decrease in the hospital stay. Most of study shows that it improves oxygenation significantly by recruitment of more atelectatic dorsal lung regions after proning. Though in a recent randomized-controlled study performed by the PALISI network in children with ALI showed no significant benefit of prone positioning (20 h/day for 7 days) on variable-frequency drives (VFDs) despite improved oxygenation, most of the intensivists prefer to keep the baby prone to improve oxygenation before considering advanced modes of ventilation.

Advanced Ventilation

*High-frequency Ventilation*¹⁸

The usual practice is to start high-frequency ventilation (HFV) in children, who fail to improve on conventional ventilation or deteriorate while on conventional ventilation. High-frequency ventilation may particularly be useful in children with air leaks—pneumothorax and bronchopleural fistulae. High-frequency oscillatory ventilation (HFOV) uses high-frequency very low-tidal volumes and laminar air flow to protect the lung. The advantage of HFOV over conventional ventilation is that it provides gas exchange at a lower airway pressure and there are smaller phasic pressure and volume changes. In a crossover trial comparing rescue HFOV with conventional mechanical ventilation in pediatric ALI/ARDS, it was found that HFOV is associated with higher mean airway pressures, improved oxygenation and a reduced need for supplemental oxygen at 30 days, however, there was not enough evidence to conclude whether HFOV reduce mortality or long-term morbidity in patients with ALI/ARDS. Two recent adult trials (OSCAR and OSCILLATE) have shown no significant differences in outcomes of ARDS, when compared to conventional ventilation, but PALICC recommended HFOV should be considered as an alternative ventilatory mode in hypoxic respiratory failure in patients in whom plateau airway pressures exceed 28 cmH₂O in the absence of clinical evidence of reduced chest wall compliance.

*Extracorporeal Membrane Oxygenation*¹⁹

Extracorporeal membrane oxygenation (ECMO) has been used as a rescue therapy for over two decades in children with ALI/ARDS with reported survival rates of 50%.²⁰ Most of the studies have shown that the survival relatively increases after early, i.e., <7 days of mechanical ventilation before the onset of significant VILI and the disease remains reversible. Still the use of ECMO is limited to those patients in whom conventional therapies have failed. Though ECMO is an effective means to keep the patient alive during severe hypoxemic respiratory failure, there is no randomized-controlled trial (RCT) defining the role of ECMO in pediatrics. According to the recent PALICC recommendation, ECMO should be considered to support children with severe PARDS where the cause of the respiratory failure is believed to be reversible or the child is likely to be suitable for consideration for lung transplantation. There exist only a handful of centers in our country those who performs pediatric ECMO due to exuberant cost and high-technical expertise.

Nonrespiratory Support

Most of the PARDS are generalized disease, where whole of the body has been affected and lungs become a part of it and some of them developed multiorgan dysfunction as well. That

is why supportive therapies are indeed necessary to augment recovery and to support the lungs.

Fluid and Electrolytes²¹

After initial fluid resuscitation for the underlying sepsis and achieving hemodynamic stability, fluid intake should be restricted to about 65–80% of maintenance fluid to minimize the capillary leak and control pulmonary edema and avoid wetting the lung further. As in adults, adverse association has been shown between cumulative fluid balance and duration of mechanical ventilatory support, success of weaning, and extubation outcomes in children. Persistent positive fluid balance is a surrogate marker of poor prognosis.

Nutrition²²

Acute respiratory distress syndrome patients are highly catabolic due to underlying primary disease process usually sepsis, and high-minute ventilation requirement of stiff lung and they benefit from initiation of early enteral nutrition. Initially, the feed can't be started as trophic feed at small volumes and monitoring tolerance and gradually build-up to the total requirement over 2–3 days. Parenteral nutrition should be initiated, if enteral nutrition is not tolerated for a few days. There is conflicting evidence in the use of fish oil omega-3 fatty acid supplementation in adults, but there is no evidence to support use of any specific nutritional formulas or supplements in children.

Analgesia Sedation

Proper analgesia and judicious use of analgesia and sedation is of prime importance for minimizing physical and mental discomfort in children. Muscle relaxants in children with ALI/ARDS should be limited. Midazolam on as required basis is the drug of choice for sedation and fentanyl or morphine for analgesia.

Judicious Transfusion of Blood Products

Try to maintain hemoglobin >10 g/dL in children with shock or profound hypoxia and >7 g/dL in children who are clinically stable. From previous studies especially with lack of supportive data for low-hemoglobin target, it is reasonable to maintain hemoglobin concentration within the normal range for age (≥ 10 g/dL) in children with profound hypoxia or shock.

Hemodynamic Support

Most of the patients of ARDS have some sort of hemodynamic instability in the form of shock. A very good hemodynamic

support in the form of inotropic and vasopressor agents should be applied depending upon the situation. Dopamine is the initial inotropic agent of choice in case of pediatric septic shock, whereas dopamine refractory cold shock needs adrenalin and warm shock needs noradrenaline.

Other Supportive Care

Care should be taken to prevent nosocomial infections. Early diagnosis and prompt treatment of these infections are crucial to their recovery.

Glucose values should be monitored regularly and consider use of insulin, if the values are persistently above 180–200 mg/dL. Very tight glycemic control is no longer preferred.

Coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding in children. Stress ulcer prophylaxis with intravenous H_2 antagonist or proton pump inhibitor or oral sucralfate is recommended. Sucralfate has some added advantage of preventing VAP by not altering gastric pH.

Routine use heparin prophylaxis to prevent deep venous thrombosis associated with central venous catheters is not routinely recommended in pediatric population. There is no data on use of heparin prophylaxis to prevent deep-venous thrombosis in critically ill children before puberty. In children beyond puberty, adult recommendations for deep-venous thrombosis prophylaxis may be relevant.

Controversial Therapies

Steroid^{23,24,20}

Corticosteroids decrease the production of a number of inflammatory and profibrotic mediators by many mechanisms, and from this theory, steroid has been tried in ARDS for several years without too much of success. A multicenter RCT was performed on the use of steroids in ARDS, which did not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. Moreover, use of methylprednisolone in late ARDS, i.e., >2 weeks after the onset of ARDS may increase the risk of death. In the landmark article by Meduri et al., they suggested a beneficial role for low-dose methylprednisolone infusion in early ARDS. There have been no studies of corticosteroids for treatment of ALI/ARDS in children, and at present there is inadequate evidence to support routine use of steroids in children with ARDS. Most of the pediatric intensivists want to reserve it for the selected patients of persistent ARDS (>7 days but <14 days) with no evidence of active infection. The dose and duration is not substantiated but starting dose with 2 mg/kg/day of intravenous methylprednisolone until extubation is the dose, which is most widely practiced.

Inhaled Nitric Oxide²⁵

Inhaled nitric oxide (iNO) is a potent and selective pulmonary vasodilator, and improve oxygenation in ALI/ARDS. It may also decrease the overproduction of cytokines in patients with severe ARDS and has also been shown to attenuate increase in capillary permeability. It may be used in patients for temporary rescue where hypoxemia is refractory to more conventional interventions. A meta-analysis of multiple studies showed that inhaled NO improved oxygenation without improving overall clinical outcomes in children and adults with ALI/ARDS and rebound hypoxia after withdrawal remains a problem. However, in children with severe hypoxic respiratory failure, iNO has been found to reduce the recruitment for ECMO. The PALICC does not recommend iNO for routine use in PARDS. However, its use may be considered in patients with documented pulmonary hypertension or severe right ventricular dysfunction. In addition, it may be considered in severe cases of PARDS as a rescue from or bridge to extracorporeal life support.

Surfactants^{26,27}

There is a meta-analysis of six trials of surfactant therapy in children with acute respiratory failure including bronchiolitis and ALI showed decreased mortality, increased VFDs and decreased duration of mechanical ventilation. Potential complications of surfactant therapy in children with ALI/ARDS may be hypotension, hypoxia, and barotrauma. At present, there is no routine recommendation of using surfactant for children with ARDS; high cost is an important issue but still in refractory cases it can be used as a rescue measure to temporary increase the oxygen demand.

The PALICC guidelines stated that surfactant therapy cannot be recommended as routine therapy in PARDS. Further study should focus on specific patient populations that may be likely to benefit and specific dosing and delivery regimens.

Prostacyclins²⁸

A few studies demonstrated that aerosolized prostacyclin may improve oxygenation in children with ALI/ARDS, but till today there is no recommendation on it.

Despite the commencement of modern therapy, the mortality of PARDS is still on the higher side. Primary ARDS due to pulmonary causes has lower mortality when compared with nonpulmonary causes. Most of patients with ARDS succumb to multiorgan failure with <5% of deaths being actually due to respiratory failure. Severity of hypoxia at the time of presentation is somehow related to the mortality. But the long-term outcome of the survivors is usually good. Further big and multicentric studies on PARDS are needed to enlighten the gray zones.

CONCLUSION

ARDS is a syndrome of pulmonary inflammation characterized by severe hypoxemia and resulting in significant morbidity and mortality. Pediatric ARDS is a distinct entity with recently revised diagnostic criteria. The management includes control of the precipitating cause, ventilatory therapy and supportive care. Low tidal volume strategy with moderate PEEP, with attention to maintain plateau pressure, is recommended, along with permissive hypoxemia and hypercapnia. A variety of rescue strategies are advocated when conventional ventilation fails. Supportive care includes attention to nutrition, sedation and analgesia and prevention of fluid overload and nosocomial infections.

REFERENCES

1. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16:428-39.
2. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334-49.
3. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149:818-24.
4. Dahlem P, van Aalderen WM, Bos AP. Pediatric acute lung injury. *Paediatr Respir Rev.* 2007;8:348-62.
5. Erickson S, Schibler A, Numa A, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: A prospective, multicenter, observational study. *Pediatr Crit Care Med.* 2007;8:317-23.
6. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med.* 2009;37:2448-54.
7. Clements RS, Steel AG, Bates AT, et al. Cuffed endotracheal tube use in paediatric prehospital intubation: challenging the doctrine? *Emerg Med J.* 2007;24:57-8.
8. Agarwal R, Reddy C, Aggarwal AN, et al. Is there a role for noninvasive ventilation in acute respiratory distress syndrome? A metaanalysis. *Respir Med.* 2006;100:2235-8.
9. Shah PS, Ohlsson A, Shah JP. Continuous negative extrathoracic pressure or continuous positive airway pressure for acute hypoxemic respiratory failure in children. *Cochrane Database Syst Rev.* 2008;1:CD003699.
10. Javouhey E, Barats A, Richard N, et al. Noninvasive ventilation as primary ventilatory support for infants with severe bronchiolitis. *Intensive Care Med.* 2008;34:1608-14.
11. Yanez LJ, Yunge M, Emilfork M, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med.* 2008;9:484-9.
12. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-8.
13. Hanson JH, Flori H. Application of the acute respiratory distress syndrome network low-tidal volume strategy to pediatric acute lung injury. *Respir Care Clin N Am.* 2006;12:349-57.
14. Miller MP, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS. *Chest.* 2008;134:969-73.
15. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev.* 2007;3:CD003844.

16. Hanson JH, Flori H. Application of the acute respiratory distress syndrome network low tidal volume strategy to pediatric acute lung injury. *Respir Care Clin N Am*. 2006;12:349-57.
17. Curley MA, Arnold JH, Thompson JE, et al. Clinical trial design—Effect of prone positioning on clinical outcomes in infants and children with acute respiratory distress syndrome. *J Crit Care*. 2006;21:23-32.
18. Arnold JH, Hanson JH, Toro-Figuero LO, et al. Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med*. 1994;22:1530-9.
19. Green TP, Moler FW, Goodman DM. Probability of survival after prolonged extracorporeal membrane oxygenation in pediatric patients with acute respiratory failure. Extracorporeal Life Support Organization. *Crit Care Med*. 1995;23:1132-9.
20. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131:954-63.
21. Randolph AG, Forbes PW, Gedeit RG, et al. Cumulative fluid intake minus output is not associated with ventilator weaning duration or extubation outcomes in children. *Pediatr Crit Care Med*. 2005;6:642-7.
22. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27:355-73.
23. Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ*. 2008;336:1006-9.
24. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1671-84.
25. Tang SF, Sherwood MC, Miller OL. Randomised trial of three doses of inhaled nitric oxide in acute respiratory distress syndrome. *Arch Dis Child*. 1998;79:415-8.
26. Duffett M, Choong K, Ng V, et al. Surfactant therapy for acute respiratory failure in children: a systematic review and meta-analysis. *Crit Care*. 2007;11:R66.
27. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA*. 2005;293:470-6.
28. Dahlem P, van Aalderen WM, de Neef M, et al. Randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury. *Crit Care Med*. 2004;32:1055-60.

Electroencephalography Monitoring in the Intensive Care Unit: Fancy Tool or Important Device?

Sunit C Singhi, Javed Ismail

INTRODUCTION

Continuous electroencephalography (cEEG) monitoring provides continuous information of brain function and thus allows early detection of neurological deterioration, which is especially useful when the clinical examination is limited. It is used in many intensive care units (ICUs) to monitor brain function in patients with altered mental status, to detect and guide treatment of nonconvulsive seizures, in the management of pharmacological coma for the treatment of increased intracranial pressure and to detect new or worsening brain ischemia in patients at high risk, and for prognostication of patients following acute neurological insult or cardiac arrest. However, there is significant interinstitutional variability in use of cEEG in different geographical regions. Some still consider it a fancy tool but recent publications show a growing evidence for use of cEEG monitoring in North America for several indications.

IDENTIFICATION AND TREATMENT OF ELECTROGRAPHIC SEIZURES AND STATUS EPILEPTICUS

Seizures are common among critically ill children. As per the clinical and electrographic characteristics, they are often classified as clinical, subtle and subclinical, or electroencephalography (EEG)-only seizures. When electrographic seizures occur without any discernible clinical correlate, they are termed subclinical or EEG-only seizures. These subclinical seizures when closely monitored represent the majority of seizures in the ICU contributing up to 70–80%.¹

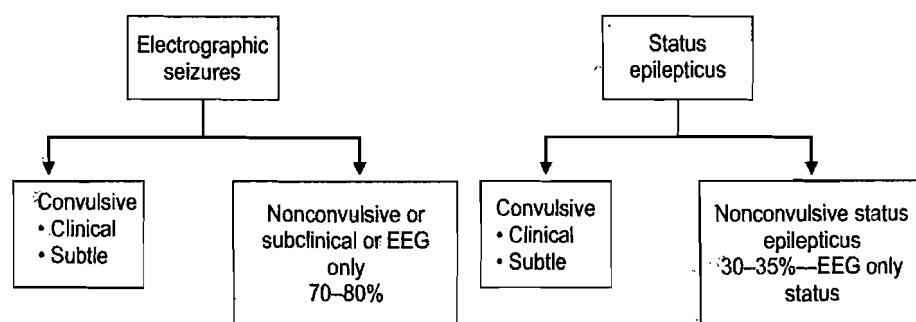
Electrographic seizures are defined as abnormal, paroxysmal EEG events that differ from the background activity, last longer than 10 seconds (unless associated with clinical signs), have a plausible electrographic field, and evolve in frequency, morphology, and spatial distribution. Electrographic status epilepticus are defined as

uninterrupted electrographic seizures lasting 30 minutes or longer, or repeated electrographic seizures totaling more than 30 minutes in any 1-hour period.

Studies have identified that 63% of children with suspected encephalitis,² 47% of those suffering a hypoxic brain injury following cardiac arrest,³ 11–20% of infants undergoing cardiac surgery,^{4,5} and 21% of children undergoing treatment with extracorporeal membrane oxygenation⁶ are at high risk of having electrographic seizures in ICU. In addition, electrographic seizures have been observed in 43–57% of children following traumatic brain injury, particularly following abusive brain trauma and when a concomitant hemorrhage is identified (Fig. 1).⁷ Furthermore, seizures are very frequently identified following childhood stroke and often represent the presenting symptom.^{8,9} The clinical factors consistently associated with electrographic seizures are persistent encephalopathy [be it in a medical ward or in the pediatric ICU (PICU)], younger age (infants <2–3 years), and the presence of clinical seizures prior to cEEG monitoring, particularly convulsive status epilepticus. About 90% of EEG seizure occur within 48 hours. It is, therefore, mandatory to monitor cEEG for 48 hours in an individual patient.

Seizures and Outcome

In a prospective cohort of 200 critically ill children, 21% had electrographic seizures and 22% had electrographic status epilepticus. The presence of electrographic status epilepticus was associated with an increased risk of mortality [odds ratio (OR) 5.1, 95% confidence interval (CI) 1.4–18.0] and an increased risk of worsening pediatric cerebral performance category (OR 17.3, CI 3.7–80.0).¹⁰ Similarly, in a retrospective multicenter cohort of 550 children, Abend et al.¹¹ demonstrated that the presence of electrographic status epilepticus was associated with an increased risk of mortality (OR 2.4, CI 1.1–5.4). However, in both these studies, the presence of electrographic seizures was neither associated



EEG, electroencephalography.

FIG. 1: Type and prevalence of electrographic seizures

with increased mortality nor worsened pediatric cerebral performance category. In a cohort of critically ill children, Payne et al. demonstrated that seizure burden greater than 12 minutes in a given hour was associated with a greater probability and magnitude of the neurological decline.¹² Also, electrographic status epilepticus has been associated with unfavorable long-term global outcome, lower health-related quality-of-life scores and an increased risk of subsequently diagnosed epilepsy.¹³ It is clear that electrocardiographic status (not seizures) affects both short- and long-term outcome in children. Treating electrocardiographic status may improve outcome in these children.

In the management of status epilepticus, titration of therapy to achieve burst suppression of EEG background has been proven to be most effective in preventing breakthrough seizures.¹⁴ Continuous electroencephalography may be helpful for adjusting infusion rates to maintain sufficient suppression while minimizing adverse drug effects. Hence, cEEG monitoring is required to identify and treat subclinical and subtle electroclinical seizures among critically ill children.

Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society recommends cEEG for diagnosis of nonconvulsive seizures, nonconvulsive status epilepticus, and other paroxysmal events, if a patient is not showing clear signs of improvement alertness within 10 minutes, or still has any impairment of consciousness for more than 30 minutes after cessation of motor or other clinically-evident seizure activity. Recording for at least 24 hours or longer is recommended. The task force also recommends cEEG for assessment and monitoring of the efficacy of therapy for seizures and status epilepticus until seizures have been controlled for at least 24 hours. A consensus statement from the neurointensive care section of the European Society of Intensive Care Medicine also recommends continuous EEG monitoring for refractory status epilepticus and suggest it for patients with status epilepticus and suspected ongoing seizures and for comatose patients with unexplained and persistent altered consciousness based on a systematic review of 42 studies.

PROGNOSTICATION

Continuous electroencephalography monitoring provides an estimate of extent of injury that can help clinicians to prognosticate and family members to make treatment decisions after acute brain injury. Burst suppression patterns after hypoxic-ischemic injury have been associated with lack of neurologic recovery.¹⁵ Electroencephalographic patterns that are not modulated by stimulation, such as alpha coma have been associated with a high likelihood of persistent vegetative state or death.¹⁶ Studies report the presence of specific EEG characteristics, like burst suppression,¹⁷ excessive discontinuity,¹⁸ severe attenuation,^{17,19} lack of reactivity,^{18,20} and periodic or multifocal epileptiform discharges,¹⁷ are associated with unfavorable prognosis. Conversely, rapid EEG improvement over hours,²¹ reactivity²² and normal sleep patterns²³ are associated with favorable prognosis. In our unit, cEEG monitoring for 24 hours using amplitude-integrated EEG (aEEG), in 30 comatose patients with underlying acute central nervous system infections, was a good predictor of outcome. Predictors of good outcome (sensitivity 93%) were presence of sleep-wave cycles and return of continuous normal voltage pattern within 24 hours of coma. Low-voltage patterns, absence of sleep-wave cycles, burst suppression, status epilepticus, and flat trace were predictive of poor outcome (specificity and positive predictive value of 96%) (Jindal A, Singhi S. DM dissertation. 2011).

IDENTIFYING ABRUPT CHANGES IN CEREBRAL BLOOD FLOW

It has been observed in studies that as cerebral blood flow decreases below 25–30 mL/100 g/min, there is a progressive loss of higher frequencies and prominent slowing of background EEG activity. Also, as the cerebral blood flow (CBF) is below 8–10 mL/100 g/min, low enough to cause irreversible cell death, all EEG frequencies are suppressed. Hence, any change in the pattern of EEG from baseline can be used as a surrogate to identify abrupt changes in CBF.²⁴

Common clinical indications for cEEG monitoring in the PICU include the following:

- Established seizures/status epilepticus, to guide titration of antiepileptic drug therapy
- Screening for subclinical seizures among patients deemed to be at high risk, for example:
 - Suspected encephalitis (bacterial, viral, or autoimmune)
 - Hypoxic-ischemic encephalopathy (e.g., neonates, cardiac arrest, and near drowning)
 - Traumatic brain injury (especially nonaccidental)
 - Stroke (ischemic or hemorrhagic).
- Screening for seizures among patients who are paralyzed and deemed to be at risk for seizures (e.g., those undergoing extracorporeal membrane oxygenation)
- Characterization of paroxysmal events suspected to represent electrographic seizures.

CONCLUSION

Electrographic seizures and electrographic status epilepticus are common in critically ill children with acute encephalopathy, often without clinical signs, and need cEEG monitoring for their diagnosis and management. Also, cEEG helps in management and prognostication of children presenting with acute encephalopathy of various causes.

REFERENCES

1. Payne ET, Hahn CD. Continuous electroencephalography for seizures and status epilepticus. *Curr Opin Pediatr*. 2014;26:675-81.
2. Gold JJ, Crawford JR, Glaser C, et al. The role of continuous electroencephalography in childhood encephalitis. *Pediatr Neurol*. 2014;50:318-23.
3. Abend NS, Topjian A, Ichord R, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. *Neurology*. 2009;72:1931-40.
4. Clancy RR, Sharif U, Ichord R, et al. Electrographic neonatal seizures after infant heart surgery. *Epilepsia*. 2005;46:84-90.
5. Helmers SL, Wypij D, Constantinou JE, et al. Perioperative electroencephalographic seizures in infants undergoing repair of complex congenital cardiac defects. *Electroencephalogr Clin Neurophysiol*. 1997;102:27-36.
6. Plantino JA, Wainwright MS, Grimason M, et al. Nonconvulsive seizures are common in children treated with extracorporeal cardiac life support. *Pediatr Crit Care Med*. 2013;14:601-9.
7. Arndt DH, Lerner JT, Matsumoto JH, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia*. 2013;54:1780-8.
8. Abend NS, Beslow LA, Smith SE, et al. Seizures as a presenting symptom of acute arterial ischemic stroke in childhood. *J Pediatr*. 2011;159:479-83.
9. Beslow LA, Abend NS, Gindville MC, et al. Pediatric intracerebral hemorrhage: acute symptomatic seizures and epilepsy. *JAMA Neurol*. 2013;70:448-54.
10. Topjian AA, Gutierrez-Colina AM, Sanchez SM, et al. Electrographic status epilepticus is associated with mortality and worse short-term outcome in critically ill children. *Crit Care Med*. 2013;41:215-23.
11. Abend NS, Arndt DH, Carpenter JL, et al. Electrographic seizures in pediatric ICU patients: cohort study of risk factors and mortality. *Neurology*. 2013;81:383-91.
12. Payne ET, Zhao XY, Frndova H, et al. Seizure burden is independently associated with short term outcome in critically ill children. *Brain J Neurol*. 2014;137:1429-38.
13. Wagenman KL, Blake TP, Sanchez SM, et al. Electrographic status epilepticus and long-term outcome in critically ill children. *Neurology*. 2014;82:396-404.
14. Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia*. 2002;43:146-53.
15. Young GB. The EEG in coma. *J Clin Neurophysiol*. 2000;17:473-85.
16. Kaplan PW, Genoud D, Ho TW, et al. Etiology, neurologic correlations, and prognosis in alpha coma. *Clin Neurophysiol*. 1999;110:205-13.
17. Kravljanc R, Jovic N, Djuric M, et al. Outcome of status epilepticus in children treated in the intensive care unit: a study of 302 cases. *Epilepsia*. 2011;52:358-63.
18. Mandel R, Martinot A, Delepoulle F, et al. Prediction of outcome after hypoxic-ischemic encephalopathy: a prospective clinical and electrophysiologic study. *J Pediatr*. 2002;141:45-50.
19. Tasker RC, Boyd S, Harden A, et al. Monitoring in non-traumatic coma. Part II: Electroencephalography. *Arch Dis Child*. 1988;63:895-9.
20. Ramachandranair R, Sharma R, Weiss SK, et al. Reactive EEG patterns in pediatric coma. *Pediatr Neurol*. 2005;33:345-49.
21. Pampiglione G, Chaloner J, Harden A, et al. Transitory ischemia/anoxia in young children and the prediction of quality of survival. *Ann N Y Acad Sci*. 1978;315:281-92.
22. Cheliout-Heraut F, Sale-Franque F, Hubert P, et al. Cerebral anoxia in near-drowning of children. The prognostic value of EEG. *Neurophysiol Clin*. 1991;21:121-32.
23. Evans BM, Bartlett JR. Prediction of outcome in severe head injury based on recognition of sleep related activity in the polygraphic electroencephalogram. *J Neurol Neurosurg Psychiatry*. 1995;59:17-25.
24. Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol*. 2004;21:341-52.

Pediatric Neuromonitoring: Electroencephalography

Saumen Meur

INTRODUCTION

Intensive and continuous hemodynamic and respiratory monitoring have been part of standard care in the intensive care unit (ICU) for a very long time now. However, continuous brain monitoring is not yet standard in most ICUs even in patients with primary or significant neurological injury. The most important reason for this is the huge complexity of the brain function and relatively few available devices, which can be used for continuous brain function monitoring until recently. Even when the devices are available the large amount of data it produces makes it difficult to interpret this data in real time. The general intensive care training also emphasizes mostly on hemodynamic and respiratory monitoring and support. Consequently, there is a significant skill and knowledge gap in monitoring and interpreting

brain function amongst the intensivists in most areas. There are controversies and areas of uncertainty including the pathological significance and treatment implications of previously undetected seizures and periodic and rhythmic patterns detected during continuous monitoring. We will review the evidence regarding the usefulness of these devices in ICU in the subsequent text.

INDICATION FOR CONTINUOUS ELECTROENCEPHALOGRAPHY

A significant number of patients both in dedicated neuroscience ICU or general ICU may benefit from continuous electroencephalography (cEEG) monitoring. Common clinical scenarios, where cEEG may potentially lead to improved clinical outcomes are listed in box 1.¹

Box 1: Indications for continuous electroencephalography monitoring

- Detection of subclinical seizures:
 - After convulsive status epilepticus
 - Following acute supratentorial brain injury with altered mental status including intracranial hemorrhage
 - Unexplained altered mental status
 - Fluctuating mental status
- Characterization of abnormal posturing and movements:
 - Episodic posturing
 - Repetitive movements
 - Unexplained tachycardia and/or hypertension in patients with actual or potential neurological injury
 - Quasinormal movements like twitching, nystagmus, chewing, or cycling movements
- Diagnosis of ischemia:
 - After subarachnoid hemorrhage
 - In patients with hemodynamic compromise with loss of autoregulation
 - During or after vascular or neurosurgical intervention
- Assessment of depth of sedation and/or anesthesia
- Confirmation of burst suppression in pharmacologically induced coma
- Prognostication

CONTINUOUS ELECTROENCEPHALOGRAPHY FOR NONCONVULSIVE SEIZURES AND NONCONVULSIVE STATUS EPILEPTICUS

A number of reliable and portable devices, which can be used bedside for continuous monitoring and display of EEG including video-EEG (vEEG), quantitative-EEG (qEEG), or amplitude-integrated EEG (aEEG) has become available in the recent years. Computer software-based interfaces which aid in analyzing and interpreting the data has also become more reliable. qEEG, for example, allows for a compressed view of hours of EEG, making it easier to visualize long-term trends. Other possible applications of cEEG include the ability to monitor and provide early detection of dynamic changes in brain functions such as ischemia. There are other devices available, which can monitor the depth of anesthesia and sedation like bispectral index (BIS), which is now in common use in anesthesia and has a potential for use in a select group of patients in the ICU as well.

The most obvious advantage of using cEEG in patients with existing or potential neurological injury would be to detect nonconvulsive seizures (NCSz) or nonconvulsive status epilepticus (NCSE). Even a convulsive seizure may be difficult to recognize in patients who are muscle relaxed, though there are likely to be other clues. In small infants and younger children it is often difficult to differentiate tonic posturing and repetitive movements from seizures.

Use of cEEG in ICUs has demonstrated that the incidence of NCSz and NCSE is much higher than suggested and detected by clinical suspicion and examination alone. Reported rates of NCS range from 8 to 37% in all ICU patients^{2,3} to 48% in patients with coma and prior convulsive status epilepticus.^{2,4-7} In critically ill pediatric patients, the reported incidence of NCSz and NCSE ranges from 7 to 4%.^{8,9}

Presence of NCSz and NCSE on cEEG has been shown to be associated with a worse outcome, independent of etiology.¹⁰ Continuous EEG in a large study (164 patients) showed continued NCSz (48% patients) and NCSE (14% of patients) even after termination of convulsive seizures. Mortality and morbidity were significantly higher in NCSE (51% mortality) or NCSz (32% mortality) group than in the no seizures on cEEG group (13%).⁴ Another study showed that increased mortality in NCSE was associated with duration of SE and delay in diagnosis only.¹¹

WHO IS AT RISK OF NONCONVULSIVE SEIZURES AND NONCONVULSIVE STATUS EPILEPTICUS?

The highest risk groups are those with altered mental status or coma and neurologic injury.^{2,3,5,6,9,12-19} Other conditions associated with a high risk of NCSz or NCSE include patients

with intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), central nervous system (CNS) infection, or traumatic brain injury (TBI), all of which have been associated with a risk of approximately 20%.^{4,5,8,20-26}

In the pediatric population NCS appears to occur most commonly in neonates with acute brain injury, especially hypoxic ischemic injury.^{8,26} In older children, NCS have been associated with a variety of diagnoses including history of epilepsy^{9,14,27} or acute presentation of epilepsy¹⁴ clinical seizure during hospital stay,^{14,19,28} TBI, hypoxic-ischemic injury, CNS infection, stroke, and metabolic disease.^{19,26-28}

HOW LONG TO MONITOR?

Classen et al. in a large retrospective review of 570 adult and pediatric patients found that only 56% of seizures were detected within the first hour, 88% within 24 hours, and 93% within 48 hours of monitoring.⁵ The same study found that patients in coma were more likely to have seizures detected later in monitoring. In comatose patients, 80% of seizures were detected after 24 hours of monitoring, 87% after 24–48 hours, and 96% after 48–168 hours. Given the current knowledge, when evaluating for the presence of NCS and NCSE, it is reasonable to monitor patients who are not in coma for approximately 24 hours and those in coma for 48–72 hours, a strategy that achieves sensitivities over 90% for seizure detection.²⁹

CHARACTERIZATION OF ABNORMAL MOVEMENTS AND POSTURING

Periodic abnormal posturing and movements like lip smacking, chewing and nystagmus are not uncommon in comatose patients.³⁰ In neonates and young infants, a range of abnormal movements like cycling type and nonpurposeful movements are common and in most cases benign. However, this may be indistinguishable from epileptiform movements and cEEG may be of useful in these scenarios.

DETECTION OF ISCHEMIA

Delayed cerebral ischemia (DCI) secondary to cerebral vasospasm is a significant cause of morbidity and mortality in patients with subarachnoid and intracerebral hemorrhage. Several studies have shown that cEEG and qEEG are very sensitive and reasonably specific in detecting DCI relatively early and before irreversible ischemic changes set in.³¹⁻³⁵ The major limitation of qEEG techniques is artefacts in recording and significant changes with pharmacological interventions. All published data are either from experimental animal models or retrospective review. However, with ongoing technological advances, real time ischemia detection with qEEG may become a reality.

MONITORING OF SEDATION OR TREATMENT RESPONSE

Response to treatment of NCSz or NCSE is equally important as there might not any other reliable clinical clue to the effectiveness of antiepileptic therapy. In these cases, cEEG is essential for detection of recurrent seizures as well as confirmation of termination with minimal effective dose. It can be useful in patients with TBI to optimize sedation to ensure reduction in metabolic rate and thereby reduce risk of increased intracranial pressure, which can lead to further injury and herniation.³⁶ cEEG can also be used to titrate the amount of drugs required to attain the desired degree of anesthesia and sedation and to minimize adverse effects associated with prolonged coma and additional sedative exposure.³⁷

In the era of therapeutic hypothermia (TH) for postcardiac arrest patients, cEEG has become an essential tool. In most TH protocols, deep sedation and muscle relaxation are warranted for at least 48 hours during which time clinical monitoring for seizure activity is very difficult. Postanoxic status epilepticus has been associated with poor outcome even after TH.^{38,39} However, early detection and treatment of postanoxic status epilepticus have been demonstrated to be associated with favorable outcome.⁴⁰

PRACTICALITIES AND LOGISTICS

There is a significant body of evidence now that suggests that cEEG monitoring is beneficial and leads to improved patient outcome in selected ICU patients. There are commercially available devices, which are reliable and can be used in routine clinical practice. However, human resources needed for real time analysis of the raw data generated from these devices remain a major hurdle. Few institutions will have round the clock electroencephalographers to analyze the data in real time. The computer-based mathematical algorithm derived qEEG, which can compress hours of raw cEEG data into two- or three-dimensional schemes can help review vast amount of data over a short period of time, but is not real time by its nature. Interpretation of these data also needs some specialist training. Seizure detection algorithms are also not sensitive or specific enough for individual patient. Furthermore, cEEG monitoring of ICU patients has also identified a number of poorly understood EEG patterns of doubtful significance. Amongst these periodic lateralized epileptiform discharges (PLED) has been most comprehensively studied, but the physiological and treatment implications of these patterns are uncertain.⁴⁰⁻⁴²

CONCLUSION

Neurological monitoring in ICUs has improved significantly over the last 2 decades. It is likely that there will be further progress in this area in the near future as well. Continuous

EEG monitoring is an integral and promising part of this process and is likely to remain so. Proving adequate trained healthcare staff to analyze and interpret this data in the clinical context at the bedside in real time; however, remains a major challenge for most institutions.

REFERENCES

1. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. *Anesth Analg*. 2009;109:506-23.
2. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology*. 2000;54:340-5.
3. Privitera M, Hoffman M, Moore JL, et al. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. *Epilepsy Res*. 1994;18:155-66.
4. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia*. 1998;39:833-40.
5. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*. 2004;62:1743-8.
6. Narayanan JT, Murthy JM. Nonconvulsive status epilepticus in a neurological intensive care unit: Profile in a developing country. *Epilepsia*. 2007;48:900-6.
7. Walker MC. Status epilepticus on the intensive care unit. *J Neurol*. 2003;250:401-6.
8. Abend NS, Gutierrez-Colina AM, Topjian AA, et al. Nonconvulsive seizures are common in critically ill children. *Neurology*. 2011;76:1071-7.
9. Shahwan A, Bailey C, Shekerdeman L, et al. The prevalence of seizures in comatose children in the pediatric intensive care unit: a prospective video-EEG study. *Epilepsia*. 2010;51:1198-204.
10. Jaitly R, Sgro JA, Towne AR, et al. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. *J Clin Neurophysiol*. 1997;14:326-34.
11. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology*. 1996;47:83-9.
12. Pandian JD, Cascino GD, So EL, et al. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. *Arch Neurol*. 2004;61:1090-4.
13. Jette N, Claassen J, Emerson RG, et al. Frequency and predictors of nonconvulsive seizures during continuous electroencephalographic monitoring in critically ill children. *Arch Neurol*. 2006;63:1750-5.
14. McCoy B, Sharma R, Ochi A, et al. Predictors of nonconvulsive seizures among critically ill children. *Epilepsia*. 2011;52:1973-8.
15. Kennedy JD, Gerard EE. Continuous EEG monitoring in the intensive care unit. *Curr Neurol Neurosci Rep*. 2012;12:419-28.
16. Jordan KG. Neurophysiologic monitoring in the neuroscience intensive care unit. *Neurol Clin*. 1995;13:579-626.
17. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology*. 1996;47:83-9.
18. Oddo M, Carrera E, Claassen J, et al. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med*. 2009;37:2051-6.
19. Williams K, Jarrar R, Buchhalter J. Continuous video-EEG monitoring in pediatric intensive care units. *Epilepsia*. 2011;52:1130-6.
20. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg*. 1999;91:750-60.
21. Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. *Neurosurgery*. 2002;51:1136-44.
22. Claassen J, Hirsch LJ, Kreiter KT, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol*. 2004;115:2699-710.

23. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology*. 2003;60:1441-6.
24. Claassen J, Jetté N, Chum F, Green R, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology*. 2007;69:1356-65.
25. Carrera E, Claassen J, Oddo M, Emerson RG, et al. Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. *Arch Neurol*. 2008;65:1612-8.
26. Saengpatrachai M, Sharma R, Hunjan A, et al. Nonconvulsive seizures in the pediatric intensive care unit: Etiology, EEG, and brain imaging findings. *Epilepsia*. 2006;47:1510-8.
27. Abend NS, Dlugos DJ. Nonconvulsive status epilepticus in a pediatric intensive care unit. *Pediatr Neurol*. 2007;37:165-70.
28. Tay SK, Hirsch LJ, Leary L, et al. Nonconvulsive status epilepticus in children: clinical and EEG characteristics. *Epilepsia*. 2006;47:1504-9.
29. Kennedy JD, Gerard EE. Continuous EEG monitoring in the Intensive Care Unit. *Curr Neurol Neurosci Rep*. 2012;12:419-28.
30. Bendbadis SR, Chen S, Melo M. What's shaking in the ICU? The differential diagnosis of seizures in the intensive care setting. *Epilepsia*. 2010;51:2338-40.
31. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. *Stroke*. 1981;12:723-5.
32. Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol*. 2004;21:341-52.
33. Claassen J, Hirsch LJ, Kreiter KT, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clinical Neurophysiology*. 2004;115:2699-710.
34. Vespa PM, Nuwer MR, Juhász C, et al. Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. *Electroencephalogr Clin Neurophysiol*. 1997;103:607-15.
35. Rathakrishnan R, Gotman J, Dubeau F, et al. Using continuous electroencephalography in the management of delayed cerebral ischemia following subarachnoid hemorrhage. *Neurocrit Care*. 2011;14:152-61.
36. Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg*. 1988;69:15-23.
37. Winer JW, Rosenwasser RH, Jimenez F. Electroencephalographic activity and serum and cerebrospinal fluid pentobarbital levels in determining the therapeutic end point during barbiturate coma. *Neurosurgery*. 1991;29:739-41.
38. Mani R, Schmitt SE, Mazer M, et al. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. *Resuscitation*. 2012;83:840-7.
39. Rossetti AO, Oddo M, Liaudet L, et al. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology*. 2009;72:744-9.
40. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol*. 2005;22:79-91.
41. Pohlmann-Eden B, Hennerici MG, Hoch DB. The relevance of post-stroke seizures. *Arch Neurol*. 2002;59:1831-2.
42. Claassen J. How I treat patients with EEG patterns on the ictal-interictal continuum in the neuro ICU. *Neurocrit Care*. 2009;11:437-44.

Section 10

Economics of Intensive Care Unit Care

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Methods of Costing in Intensive Care

Atul P Kulkarni, Natesh R Prabu

INTRODUCTION

Healthcare for critically ill patients has improved due to better understanding of disease process and advancement in technology. The healthcare cost for critically ill patients are expensive due to increasing expectations, involvement of multidisciplinary team, varied application of technology, increased aging populations and a large requirement of trained man power. The utilization of intensive care unit (ICU) services is varied and versatile, which depends upon diagnosis, severity of illness, and length of stay.^{1,2}

Intensive care unit comprises less proportion of hospital beds but imposes huge burden on the hospital's operational cost. Patients, who survive critical illness impose additional cost burden on both the hospital and the individual citizen. It's high time to achieve a balance between health expenditure and quality-of-care being provided to critically ill patients. Therefore, knowing the expenses and steps to reduce costs in running an ICU becomes vital.

WHAT IS COSTING?

Cost is a resource once allocated cannot be reallocated to alternate purpose.³ Cost is measured in monetary units and always involves acquisition costs and additional operational or utilization costs. Costs includes the quantity of all resources utilized and the price of each resource, i.e., usage \times price.

WHY COSTING IS IMPORTANT?

Intensive care unit care is labor intensive and expensive, where quality-of-care cannot be compromised and cost differs between individual patients. It offers round the clock service to patients consuming enormous resource contributing around 4–6 times more cost per day compared to cost in general ward. Each ICU receives a particular group of patients and has different staff-patient ratio, bed strength, occupancy ratio and varied technology usage.^{1,2} The costs of

services depend upon the outcome measure like mortality, length-of-stay, etc.² Cost is usually defined for a particular time frame, i.e., cost per day, cost per month, cost per year etc. so that changes in cost can be tracked and cost plan can be further modified according to the needs.⁴ Estimating the cost of intensive care is therefore important for proper allocation of resources and budget.

UNDERSTANDING DIFFERENT COSTS (TABLE 1)

Costs spent on intensive care of patients are grouped into those, which are spent directly for patient care and those that are spent indirectly.⁴ The costs vary between initial days of intensive care and for every additional days of ICU stay. Certain costs depend upon the patient volume and vary from time to time and patient to patient.

Costs are of four major types:

1. Direct fixed and direct variable (contribute to majority of costs)
2. Indirect fixed and indirect variable.

Direct Cost or Patient-related Costs

Direct costs are costs those are fully and directly attributed to patient care, e.g., administering blood products, intravenous

TABLE 1 Different costs: classifying the costs spent on dialysis training for intensive care unit technicians and physicians

	Direct costs *	Indirect costs
Variable costs	Dialysis fluid, dialysis catheters	Annual maintenance, repairs of machines
Fixed costs	Acquisition or capital	Training given to technician and physician (independent of patient volume and not related patient care)

fluids, and usage of disposables. In economic terms, direct costs are the costs of all services, utilities, and resources involved in provision of patient care.

Indirect Cost or Nonpatient-related Costs

Indirect costs those are shared among patients and may not directly be involved in patient care, e.g., warming of intravenous fluids, physician's time other than bedside, and cleaning the ICU.

Fixed Costs

Fixed costs are cost spent independent of patient volume. The resource will be utilized by all patients and does not depend on number of patients getting treated. These costs reflect the structural quality of ICU and cannot be modified or controlled. Majority of cost in running ICU is spent on fixed costs for example costs of building, monitors, acquisition cost of instruments, etc.

Variable Costs

Variable costs are the costs that depend on volume of patients treated. It varies with every additional patient and is associated with the process of delivering the patient care, e.g., gloves and syringes.

Other Cost Types

Another type of cost is marginal cost, i.e., cost spent for each additional day in ICU. It is different from average cost per day since cost during initial days of ICU stay will be much more than later days. So the cost savings to the hospital associated with reducing ICU length of stay by one day will be negligible.

Opportunity Costs

It refers to alternate uses for resources or money spent. The money spent on one resource cannot be utilized for other purposes. Once money is spent on buying something, it is not available for other purposes. The opportunity cost of buying a cardiac output monitor might be a new ultrasound machine that would have been used in other parts of the hospital as once money is spent on cardiac output monitor it cannot be used to buy ultrasound machine. Opportunity cost is difficult to measure and does not directly involve the running of the ICU or treating the patient.

ASSESSMENT OF COSTS

Costs can be measured by collecting and summing various cost types. This will give the total cost. The cost can be as cost per patient per day or cost for hospital acquired infections or cost for running the ICU. Assessing the cost in intensive care

is a difficult task since there is no standard methodology⁵ and heterogeneity in resource allocations and critical care utilization (demand:supply ratio) varies among different nations and regions.

APPROACHES TO COST ALLOCATION

Approaches to cost allocation can be of two types:

1. Direct measurement of cost—where actual expenses are measured
2. Indirect or proxy measurement—where surrogate markers of expense are substituted for cost.

DIRECT MEASUREMENT OF COST

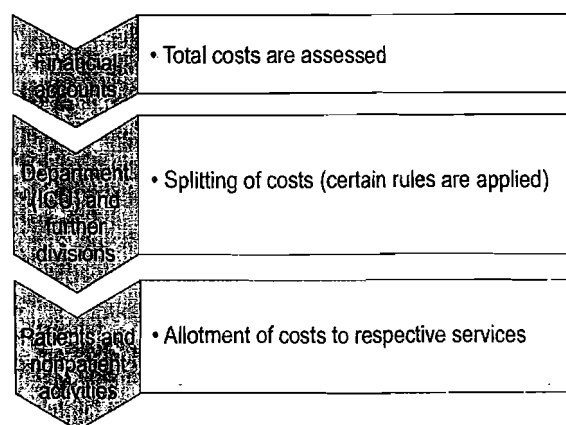
Top-down Approach (Attributable Costing) (Fig. 1)

In this method,^{4,6,7} total hospital costs are collected and split to the level of respective services. In regard to intensive care, the costs are calculated by dividing the total intensive care budget by the number of patients or patient-days in ICU to derive an average cost per patient-day. This is an easier method to compute cost. The total cost is allocated to all patients and gets divided among individual patients. The allocation of resources does not take into account the variation in expenses between individual patients, which may be large. So, no allocation can be done for individual patients, diseases or procedures.

Top-down costing can only be done retrospectively since information is commonly obtained from accounts department and used for allocating indirect costs like housekeeping, capital costs, etc.

Bottom-up Approach (Microcosting) (Fig. 2)

Bottom-up⁷ means collecting costs at patient level. All resources that are used for patient care are collected and



ICU, intensive care unit.

FIG. 1: Steps involved in top-down approach

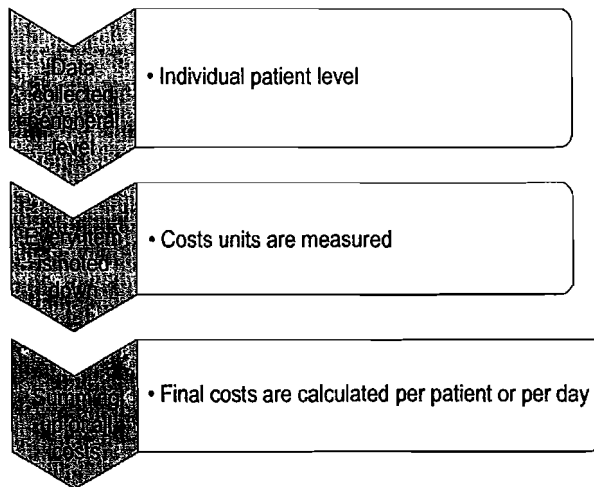


FIG. 2: Steps involved in bottom-up approach

summed up to get final cost spent on individual patient. This is commonly done prospectively in real time while patient is in ICU, but may also be done retrospectively (using patient records). Cost is allocated to individual patients based on the use of individual resources. In bottom-up approach, the data collection is labor intensive, more time consuming, expensive, and often incomplete when indirect costs are concerned. In bottom-up approach the costs are compiled by “costs units”, i.e., cost of a single item is multiplied with units of resources used. Bottom-up method allows for detailed analysis and helps to segregate costs based on specific patient subgroups. This method does not account for fixed costs and overheads, because they are dependent on ICU organization and cannot be accurately charged to one patient.

ALTERNATIVE COSTING METHODS (PROXY MEASURES)

Cost Block Method

Cost block system is a type of top-down approach developed by Intensive Care National Working Group in Costs in the United Kingdom. The annual costs of ICU are divided into six defined categories costs called as “cost blocks”.⁸

The six cost blocks are listed as follows (contribution to total costs is given as percentage):⁹

- Cost block 1: Capital equipment—6.0%
- Cost block 2: Estates (the fabric of building including maintenance, depreciation, utilities, water, sewage, and waste disposal)—2.7–3.4%
- Cost block 3: Nonclinical support services (cleaning and administration)—7–7.8%
- Cost block 4: Clinical support services (e.g., laboratory services, physiotherapy, occupational therapy, and dietetics, radiology)—7–8.5%
- Cost block 5: Consumables (e.g., drugs, syringes, and other disposables)—21.5–24.7%
- Cost block 6: Staff (doctors, nursing staff)—53.6–54.7%.

The cost block approach has been validated in further studies in UK. Patient related costs (i.e., cost block 4–6) accounted for around 85% of total costs and remaining 15% for nonpatient related costs. The nonpatient related costs (i.e., cost block 1–3) are relatively fixed without much change. Cost block methodology based on patient-related costs consisting of cost blocks 4–6 were commonly used to collect data of ICU in United Kingdom.

ACTIVITY-BASED COSTING

This is a form of bottom-up costing in which, for each activity of care, the resources necessary to deliver that activity are identified. The activity-based system measures patient-related cost of delivering care. Example, for delivering an antibiotic, the activities involved are staff time, syringe and needle time, dilution of drug, administration of drug, charting of drug. The total cost of the activity is the sum of the costs of individual components. There are three types of activities involved:

- Start-up costs—determined from the resources necessary to initiate an activity of care, e.g., insertion of a pulmonary artery catheter (PA catheter)
- Point costs—determined by the resources used in discrete events or procedures, which occur in the delivery of an activity of care, e.g., the staff cost of taking a measurement from PA catheter
- Interval costs—these are measured as a cost per hour and are determined from the resources necessary to cover the increased level of ongoing care necessary to maintain an activity, e.g., the staff cost of routine care of PA catheter.

All activities involve at least one of the three costs. The cost of patient care is thus determined by allocating resources for each activity involved.

OTHER PROXY MEASURES

The process of calculating costs for individual patients is a tedious one; hence, various surrogate measures have been developed as substitutes for actual costs.^{4,10} Some of these include:

- Hospital charges—collecting the charges and summing up the charges will give total cost spent. This method is popular in the United States; however, charges do not always accurately represent expenses incurred
- Weighted hospital days—these provide a length-of-stay index. However, importance given to individual days of stay is arbitrary and cannot be generalized
- Diagnosis-related groups—payment is based on calculation of average costs from a large number of patients with a similar diagnosis. The disadvantage of this method is that in ICU, the diagnosis is not always apparent and cost of care may vary significantly even among patients with the same diagnosis
- Healthcare resource grouping—this is a new strategy, which aims to identify patient groups of clinical similarity.

Resources allocation will be similar for particular group of patients

- Severity of illness—allocation of ICU costs could be based on the severity of the patient's illness as determined by severity scores such as APACHE II or SAPS II
- Activity related—activity scores such as the Therapeutic Intervention Scoring System (TISS) could be used to assess ICU costs.

HEALTH ECONOMIC ANALYSIS

Health economic analysis^{7,11-13} in intensive care is important since it is a lot more expensive. It is important to know whether the expected health intervention justifies additional cost. The budget allocated to run ICU is often limited, creating more pressure on the administrator for cost containment. Accurate cost information allows improved decision making in terms of resource allocation, expanding, and maintaining existing medical services.

The health economic analysis allows choosing cheaper and most effective interventions thus reducing costs.

Methods of Economic Analysis

The four basic methods are as follows:

1. Cost benefit analysis
2. Cost effectiveness analysis
3. Cost utility analysis
4. Cost minimization analysis.

Cost-benefit Analysis

Costs and benefits both are calculated in monetary terms. The analysis is interested in net gain or net loss (in money). In patient care, it is a less used method.

Cost-effectiveness Analysis

Cost effectiveness refers to combined clinical and economic value of particular intervention or program. Costs are measured in terms of money and benefits in terms of outcome, i.e., life years saved. This analysis helps to compare two or more interventions for defined outcome and attempts to answer whether the intervention concerned is worth doing. The measurements used are cost-effectiveness ratio (money saved per year of life saved) and marginal cost effectiveness ratio (change in money spent/change in years of life saved). The majority of ICU interventions are expensive and it is important to analyze whether the additional cost associated with intervention is resulting in improved survival, i.e., incremental cost is associated with incremental benefit. The ideal intervention should be less costly and more effective. The cost-effectiveness analysis answers whether a new intervention should be introduced when compared to doing nothing or other alternatives.

Cost Utility Analysis

Cost utility analysis is a variant of cost effectiveness analysis where costs are measured in monetary terms and outcome in quality-adjusted life years (QALY). The measurements used are cost utility ratio (cost per QALY). The common reported outcome is incremental cost per QALY gained.

Cost Minimization Analysis

Cost minimization analysis is a basic and commonly done analysis where analyst is interested in saving cost. The cost minimization analysis compares only in financial terms of interventions with equal effectiveness.

CONCLUSION

The costs calculation and cost analysis are becoming integral part of running ICU due to unavoidable increasing ICU costs, limitation of resources and need of high-quality patient care. Top-down method is easy to compute costs at macrolevel and should be used until detailed analysis of costs is required. The critical care physician should be aware of expenses and choose more cost-effective intervention.

REFERENCES

1. Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care: methods and human and capital inputs. *Crit Care Med.* 1996;24(7):1168-72.
2. Slonim AD, Pollack MM. An approach to costs in critical care: macroeconomics versus microeconomics. *Crit Care Med.* 1999;27(10):2286-7.
3. Horngren CT, Bhimani A, Foster G. Management and cost accounting. Prentice Hall, London, UK; 1999.
4. Jegers M, Edbrooke DL, Hibbert CL, et al. Definitions and methods of cost assessment: an intensivist's guide. ESICM Section on Health Services Research and Outcome Working Group on Cost Effectiveness. *Intensive Care Med.* 2002;28:680-5.
5. Jacobs P, Noseworthy TW. National estimates of intensive care utilization and costs: Canada and the United States. *Crit Care Med.* 1990;18(11):1282-6.
6. Gylmark M. A review of cost studies of intensive care units: Problems with the cost concept. *Crit Care Med.* 1995;23(5):964-72.
7. Seidel J, Whiting PC, Edbrooke DL. The costs of intensive care. *Continuing Education in Anaesthesia, Critical Care and Pain.* 2006;6(4):1-4.
8. Edbrooke D, Hibbert C, Ridley S, et al. The development of a method for comparative costing of individual intensive care units. *Anaesthesia.* 1999;54:110-20.
9. Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care: methods and human and capital inputs. *Crit Care Med.* 1996;24(7):1168-73.
10. Stevens VG, Hibbert CL, Edbrooke DL. Evaluation of proposed case-mix criteria as a basis for costing patients in the adult general intensive care unit. *Anaesthesia.* 1998;53:944-50.
11. Heyland DK, Konopad E, Noseworthy TW, et al. Is It 'Worthwhile' To Continue Treating Patients With a Prolonged Stay (>14 Days) in the ICU? An Economic Evaluation. *Chest.* 1998;114(1):192-8.
12. Coughlin MT, Angus DC. Economic evaluation of new therapies in critical illness. *Crit Care Med.* 2003;31(1 Suppl):S7-16.
13. Rapoport J, Teres D, Lemeshow S, et al. A method for assessing the clinical performance and cost-effectiveness of intensive care units: a multicenter inception cohort study. *Crit Care Med.* 1994;22(9):1385-91.

Attributable Cost of Hospital-acquired Infection

Prakash Shastri

INTRODUCTION

Hospital-acquired infection (HAI) has assumed epidemic proportions in the intensive care units (ICUs) worldwide. Hospital-acquired infection is a major problem that prolongs hospital stay and places a huge burden on ICU resources. Prevention requires a system-wise approach, and many prevention strategies are effective. It is intuitively believed that increasing investment for infection control is economically justified.¹ Optimal analytic methods should be used to estimate the primary economic parameters. The primary reason to understand the cost of an HAI is to inform decisions about how to reduce the problem.²⁻⁵ Because healthcare resources are scarce, HAIs should be reduced by allocating resources only to efficient infection control programs. The main cost of an HAI is the extra stay in hospital. Estimates of extra length of stay based on sounder statistical methods tend to show a shorter estimated extra stay, which means that the cost of an HAI may have previously been overestimated.⁶ Also problematic is the method used to attach monetary value to lost bed-days, which is often based on cost accounting practices and not economic principles.

COSTS ASSOCIATED WITH HOSPITAL-ACQUIRED INFECTION (BOX 1)

To provide a comprehensive picture of the burden of HAI, all costs should be considered. Researchers working in the area of HAI rarely include costs that fall outside the hospital sector.

METHODS OF COST ESTIMATION

Extra number of hospital days more than the average in HAI patients may be the easiest and simplest of estimating the attributable cost of HAI. These estimates are not very accurate and probably only help in raising the awareness of this issue of extra health care. There are other ways of estimating attributable cost of HAI, e.g., concurrent and comparative methods.

In the concurrent method, appropriately trained staff is needed for cost estimation purposes. Wakefield et al.⁷ used this method with trained personnel who assessed each day in a protocolized manner whether the reason of extra hospital stay was due to HAI or underlying disease process or both. In the comparative method, resource allocation is estimated after HAI patients were matched with controls as regards the confounders in resource allocation such as age, gender, underlying diagnosis, treatment received, and comorbidities.⁸ Hyryla and Sintonen⁹ and Plowman et al.¹⁰ similarly studied prospectively a cohort of patients and documented their HAI status and hospital cost and used a regression model, along with other control variables, in order to identify the effect of HAI on cost outcome. This is more labor intensive but more accurate approach for true cost estimation attributable to HAI, in which controls are properly matched and confounding variables are accounted for and a level of significance with confidence interval around the estimate is available to get an idea of the spread of attributable cost due to HAI.

Another important issue in estimating attributable cost due to HAI is to have an estimate of the baseline cost. Usually, the same cost for each hospital day is assumed which is

Box 1: Costs associated with hospital-acquired infection

- Opportunity costs to health services
 - Hospital services inpatient stay (inpatient days, investigations, treatments)
 - Outpatient consultations (consultations, investigations, treatment)
 - General practitioner (consultations, investigations, treatment)
 - Private nursing and other (nursing care, investigations, treatments)
- Private costs to patients and informal carers
 - Out of pocket expenditures (travel, medicines, miscellaneous expenses)
 - Other consequences (death, anxiety, pain/discomfort)
- Other costs to society
 - Production losses due to inability to earn

erroneous. Moreover, this method does not take into account other confounding variables for resource allocation like age, diagnosis, infection status, etc. This method might conceal the real pattern of resource use.

Haley et al. have advocated another method of micro-costing.⁸ In this method, the various components of patient care are accounted for, and estimates of cost are made for each of them. In another study¹¹ using microcosting method, all the resources used by patients were assessed including information of all laboratory, pathology, procedures, and imaging tests. The cost estimates of these resources were done. Hospital overheads, capital assets, and management function tests was also taken into account and attributed to the patient. This method takes into account the opportunity cost of using hospital resources.

One more approach is to maximize the amount of health gained from a defined pot of resources. This is called an extra-welfarist view of economics¹² and is used widely in health services decision making.¹³

The extra-welfarist approach uses a conceptually simple rule to guide decision making. The change to cost from a decision to adopt a new health intervention (such as a novel infection control intervention) should be adequately compensated by the change to health benefit. Changes to cost are summarized in monetary terms, and changes to health benefit are normally described by means of quality-adjusted life-years (QALYs), which combine information on the quantity and quality of years of life gained.¹⁴ The number of QALYs gained from infection control demonstrate improved quality of care, because lives are saved, and events that reduce the quality of life for hospital patients are avoided.

HOSPITAL AND COMMUNITY HEALTH SERVICE COSTS

Plowman et al. reported costs borne by patients both in and outside the inpatient hospital sector with predominant cost borne by the inpatient sector.¹⁰ The limitation of this report was that it was restricted to certain specialties only constituting 70% of all admission and cannot be generalized to all inpatient disciplines, where the cost estimates could be considerably higher.

CONCLUSION

The policy makers need guidance regarding investment in infection control by appropriate estimation of attributable cost of an HAI and benefits that can be gained by such investment. Thus, an infection control program could save substantial amount of money by avoiding, say 20 infections, and these infections had an attributable cost of ₹ 10,000. The hospital could have net benefit by investing into infection control program with cost of investment less than ₹ 100,000. With rigorous evidence-based cost estimation models, one can influence the policy makers in appropriate allocation of hospital budget.

REFERENCES

1. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. *J Hosp Infect.* 2003;54:258-266.
2. Stone PW, Braccia D, Larson E. Systematic review of economic analyses of health care-associated infections. *Am J Infect Control.* 2005;33:501-9.
3. Stone PW, Larson E, Kowar LN. A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990-2000. *Am J Infect Control.* 2002;30:145-52.
4. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the economic evaluation of health care programme.* 3rd edition. Oxford, UK: Oxford University Press, 2005.
5. Graves N, McGowan JE. Nosocomial infection, the deficit reduction act and incentives for hospitals. *JAMA.* 2008;300:1577-9.
6. Barnett AG, Batra R, Graves N, et al. Using a longitudinal model to estimate the effect of methicillin-resistant *Staphylococcus aureus* infection on length of stay in an intensive care unit. *Am J Epidemiol.* 2009;170:1186-94.
7. Wakefield DS, Ptaller MA, Hammons GT, et al. Use of the appropriateness evaluation protocol for estimating the incremental costs associated with nosocomial infections. *Med Care.* 1987;25:481-8.
8. Haley RW. Measuring the costs of nosocomial infections: Methods for estimating economic burden on the hospital. *Am J Med.* 1991 Sep 16;91(3B):32S-38S.
9. Hyryla MLJ, Sintonen H. The use of health services in the management of wound infection. *J Hosp Infect.* 1994;26:1-14.
10. Plowman R, Graves N, Griffin MA, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *J Hosp Infect.* 2001;47(3):198-209.
11. Plowman RP, Graves N, Griffin M, et al. *The Socioeconomic Burden of Hospital Acquired Infection.* Public Health Laboratory Service, London; 1999.
12. Cookson R. Willingness to pay methods in health care: a sceptical view. *Health Economics.* 2003;12:891-4.
13. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. *J Am Coll Cardiol.* 2008;52:2119-26.
14. Brazier J, Deverill M, Green C, et al. A review of the use of health status measures in economic evaluation. *Health Technol Assess.* 1999;3:i-iv,1-164.

Cost Minimization in Intensive Care Unit

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INTRODUCTION

The cost of intensive care is widely recognized as being both expensive and increasing.¹ It is estimated that there are about 70,000 intensive care unit (ICU) beds available including all types and across all hospitals and small-time nursing homes in India that cater to 5 million patients requiring ICU admissions every year.² India currently spends ₹1,030,000 million on healthcare, which is projected to grow to ₹2,830,000 million by 2012,² intensive care accounts for 20–30% of a hospital's budget.² In the absence of comprehensive insurance cover, >80% patients have to pay out of their pocket for healthcare services. The burgeoning cost of intensive care encompasses the capital equipment, estates, nonclinical support services, clinical support services, consumables, and manpower costs. Cost minimization is a pharmacoeconomics tool, which can be applied across various facets of care delivery in an intensive care one of them being comparing two drugs of equal efficacy and equal tolerability.

DEFINITION

Cost-minimization analysis measures the differences between two alternative interventions with an assumption made that both the interventions are equally effective and difference exist only in the cost.³ Costs are compared with an assumption that the intervention with lower cost is adopted.

COST ANALYSIS PERSPECTIVE

Cost analysis perspective could be healthcare related including patient and ICU variables and society related, which is considered the gold standard. Example of former includes conducting an economic evaluation of early goal-directed therapy (EGDT) from an ICU's perspective, only costs incurred by the ICU are included. Such costs may include personnel (medical, nursing, and allied health), clinical support services (such as radiology and pathology), consumables (such as medications, clinical supplies and

nonclinical supplies), and capital equipment costs. However, if conducting the analysis from a societal perspective, all costs (and benefits) should theoretically be included, regardless of who incurs the costs (or receives the benefits). Therefore, costs borne by patients and their relatives such as the costs of transport to healthcare appointments and lost wages should be included, as should the costs to the patient's employer as a result of the patient being absent from work. In a systematic review of the critical care cost-effectiveness literature, only 2 of 19 identified analyses conducted their evaluation from a societal perspective with all others conducted from a healthcare perspective.⁴

IDENTIFYING ALTERNATIVES

Cost-minimization analysis involves comparison of two or more interventions. Newer interventions are compared with current practice, which becomes a comparator, e.g., dexmedetomidine versus midazolam as a tool to reduce delirium and duration of mechanical ventilation. Choosing the right alternative for the purposes of comparison is important. Comparing a new intervention to a costly or inefficient practice may artificially infer a new intervention is highly cost-effective. Likewise, comparing a new intervention to an out-of-date or little used intervention will not provide results that are generalizable to the broader population that may be the target of the intervention.

COST OF INTENSIVE CARE: GENERAL PRINCIPLES

Every intensivist should actively be involved in understanding the costs in their individual unit and how it relates to therapeutic activity, case mix and clinical outcome. This would help to allocate resources efficiently, thereby improving the volume and quality-of-care.

In general, there are two methods of costing described as "top down"² and "bottom-up"⁵ method; each having its advantages and disadvantages. There are six cost blocks

identified in intensive care, which include (i) staffing costs, (ii) clinical support services, (iii) nonclinical support services, (iv) consumables cost, (v) real estate costs, and (vi) major capital equipment. The capital costs were converted into dollars using the purchasing power parity, which allowed for the first time, the comparison of ICU costs from one country to another using common reference point.⁶

COST OF INTENSIVE CARE IN INDIA

One reference study done in India more than 10 years back by Parikh and Karnad⁷ showed that ICU cost per patient per day was ₹1973, which is far less compared to the current prevailing cost. Current cost for a patient in tertiary referral ICU in any of the metro city in India per day ranges anywhere between ₹20,000 and ₹40,000 or more. The authors in their study have expressed their opinion on reuse of sterilized material, which were meant to be single use as a cost-minimization measure commonly practiced in Indian hospitals. One such example being reusing percutaneous tracheostomy set up to 3–4 times after sterilization, which may curtail the consumable cost to the patient.

It was also shown in the study that unit which functions as closed unit with good resident staff coverage significantly improved quality-of-care and effective resource utilization.⁸ One of the limitations of this study showing significantly low-ICU cost could be attributed to 65% of patients in this study were referred from other hospitals after undergoing treatment for 2–7 days. It has been shown clearly that resource utilization and increased costs in ICU occur during the early phase of ICU care typically the first 2–3 days.⁹

COST-BLOCK ANALYSIS AND COST-MINIMIZATION VARIABLES

Capital equipment comprises two-thirds of the established cost in intensive care. Indigenizing the equipment, procuring the equipments from local manufacturers albeit not compromising on the quality, if available, and minimizing the import of equipment has achieved significant cost minimization. Indian manufacturers of medical devices and equipment have been steadily growing in last decade with major International manufacturers setting up a local base. Most imported equipments are well subsidized given the sheer volume of business they are exposed to in a populous country like India. Indian Society of Critical Care Medicine guidelines advocate the consultant intensivist to have a clear role in the choice of equipment and recommend that the intensivist would not compromise on the quality in an attempt at cost minimization or profit maximizing. Another innovative measure toward cost minimization would be sharing a pool of equipment between ICUs in a common geographical location or leasing the equipment.

Estate costs hugely vary between different geographic locations and within a city. Due to increased heterogeneity in this area, factoring in this cost and measures of cost minimization in this block is difficult. The components of nonclinical support services include catering, cleaning laundry, uniform, administration costs of the staff employed by the ICU, and miscellaneous expenditure such as stationery, telephone, photocopying, etc. Comparable data from other industries such as information technology and banking reveals a low investment, operating, and maintenance costs for these categories in India. It is unlikely to be different in healthcare industry and contributes less toward overall ICU costs.

Clinical support services are directly related to patient therapy but are not supplied by the ICU. It includes all services rendered to ICU patients from outside ICU like physiotherapy, radiology, dieticians, and other specialty clinical services such as cardiology, nephrology, and laboratory services. Comparative figures from the United Kingdom showed that this block constitutes 5–7% of the total ICU resource utilization.¹⁰ There is increasing evidence that closed ICU^{8,11–14} has better outcome and resource utilization than open ICUs translating to cost minimization. In an open ICU, increasing number of clinical support services will be adding to the overall costs.

Manpower cost is defined as net pay out for medical and nursing staff employed fully or partially in ICU. Figures from the West quotes a high percentage (about 50%) of the total costs of ICU which are clear reflection of the labor-intensive requirements as well as high level of remuneration for both medical and nursing staff within critical care.¹⁰ However, this is different in India with low-staff wages as shown in study by Parikh and Karnad resulting in lower cost to this block. On the flip side, high level of attrition, increased workload, and migration to other countries create an ongoing shortage and demand for support staff, which in turn affect quality-of-care and hence possible costs.

Consumables will be the major determinant toward the total cost. Parikh and Karnad concluded that low cost of ICU care in India is partly because of low cost of generic drugs and recycling of consumables. Though the latter still holds true, the cost of drugs has increased enormously. This is a strong reason for the intensive care specialist to strictly adhere to evidence-based medicine when rationalizing the usage of drugs and look at avenues for effective cost-minimization measures, which will immensely benefit the patient. The number of drugs used in ICU increases with the duration of stay. It was noted that mean number of drugs on admission was 5.3, which increased to 12.9 on day one and 22.2 during the entire stay.¹⁵ Expenditure on antibiotic accounts for almost 50% of ICU cost in India. Moreover, inappropriate use of broad-spectrum antibiotic is leading to increased incidence of multidrug-resistant bacteria in ICU.^{16–20}

SHORT-CYCLE IMPROVEMENT METHOD FOR COST MINIMIZATION

This method includes identifying areas of improvement, defining mechanism to evaluate outcome, and initiation of improvement plan.²¹ This cycle is repeated with new adjustments to improve the outcome. Baseline data on areas for improvement is prospectively collected and protocols to initiate change are developed and tested by short-improvement cycles. Outcomes are evaluated, protocols are modified, and another cycle is performed.

This method was validated in a study by Marx et al. in which three areas of improvement were identified: (i) standing orders for routine laboratory tests, routine electrocardiogram and daily chest X-ray were eliminated, (ii) protocol for sedation, analgesia and neuromuscular blockers were implemented, and (iii) protocols for weaning from mechanical ventilation.

By this kind of protocolized care cost, saving was achieved in many aspects, e.g., laboratory tests were reduced by 65%, chest X-ray imaging was reduced by 56%, neuromuscular blocking agents cost was reduced by 75%, and ventilator hours were reduced by 35%. These resulted in decreased length of stay (LOS) by 1.5 days with cost savings of 4% per patient per day annually. There was an added advantage of decreased incidence of nosocomial infection with no significant difference in the mortality from baseline.

RATIONING AS A TOOL FOR COST MINIMIZATION²²

Caveats of cost minimization in critical care include difficulties in estimating marginal costs of critical care treatments, limited evidence for any treatments with efficacy, and the ethical principle of rescuing identifiable lives in imminent risk of death. Given the burden of critical illness and the wide variation in resources a global approach to rationing is untenable.

Allocation

High-ICU costs are driven by the use of high technology and its labor-intensive area nature of healthcare. However, there is lack of evidence for many intensive care services, including evidence supporting criteria for ICU admission. Certain decisions in ICU, like not prescribing antibiotics for a presumed viral infection, are the sort of healthcare rationing decision with clinical consequences.²³

Allocation decisions are sometimes subtle and may be taken when there are no limitations on the alternatives, which might be an expensive option but more beneficial for the patient. Examples of such allocation decision could be use of cheaper antibiotic and other drugs, nurse to patient ratio, or use of an ICU bed in cases of small benefit, for example patients at low risk of complications. Allocation

decisions bring two major ethical conflict can occur with these allocation decisions. The physician may act in the best interest of patient following ethical principle of beneficence, whereas the ethical principle of justice may lead clinicians to act fairly.²⁴ For example, triage, prioritization, and cost-effectiveness are all some form of allocation decision.^{25,26}

Allocation versus Evidence-based Medicine

Decisions, which are predominantly evidence based, are not rationing decisions. These interventions are often termed futile, medically inappropriate, or experimental.^{25,27} For example, withholding transfusion for hemoglobin of 7 g/dL is not rationing blood because there is evidence that blood transfusion above this limit may be harmful.²⁶ Similarly, decision not to use human growth hormone, which is expensive, is not a rationing decision because this treatment has not been shown to be ineffective and may be harmful.²⁸

There are various factors that influence clinician's assessments of risk benefit balance of various interventions. These may include the value the clinician assigns to being wrong, objective evidence viewed with subjective values and biases, the value assigned to trying to "rescue" a patient in imminent danger of death; the clinician's tolerance for uncertainty; the impact of the decision on the clinician's finance; biases about the patient's age, gender, race, functional status as well as the cost or availability of the resource.^{29,30} Transition from summary of evidence to cost-based recommendations are subtle. For example, the authors of a recent systematic review of colloid resuscitation in critical care conclude that "there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death compared to crystalloids in patients with trauma, burns and following surgery."³¹ This is a statement of their summary of evidence of efficacy. Like many treatments in the critical care, the evidence neither supports nor completely refutes the use of colloids as resuscitation fluids in the critically ill. However, the authors conclude, "as colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patient types can be justified outside the context of randomized controlled trials." Although the first statement may be a fair summary of the evidence, the recommendation against using colloids in the second sentence is fundamentally a rationing or allocation assessment based on cost-effectiveness. It incorporates an implicit strategy that recommends only treatment that has demonstrated benefit related to their cost. Although one might conclude from the author's review that colloid resuscitation is experimental or that its benefit is likely to be small, the reasoning for recommending against its use is based on the cost of the treatment. This example shows how assessments of cost can creep into evidence-based recommendations for therapy, even without formally discussing allocation. Clinicians may find decision of futility

or appropriateness less ethically problematic than decisions made factoring in the cost and rationing.

Treatments, those are risky and expensive, will require more evidence to convince physician to adopt it in practice than treatments those are safe and cheap. Head of bed elevation to prevent ventilator-associated pneumonia in mechanically ventilated patients, as it is safe and inexpensive, it has been adopted widely though the evidence supporting its benefit in hard endpoints like decreasing mortality or reducing ICU LOS is limited. On the other hand, expensive interventions like kinetic beds, topical prophylactic antibiotics and special endotracheal tubes are used less commonly despite evidence supporting their use. Thus making allocation decision, which is objective, explicit and transparent should take into account the complexity of assessing efficacy and cost.

Illusory Cost Savings

Since the earliest days of intensive care, technological, workforce and organizational innovations have been proposed as opportunities to reduce the exorbitant cost of critical care. In 1972, an optimistic author wrote, "The more promising approaches to cost reduction are all in an early stage of development now. Both deprofessionalization of the ICU by wider use of allied health personnel and the automation of therapeutic functions are just beginning to be applied."³² Despite implementation of both of these measures, there is little evidence that cost increases in hospital- or ICU-based care have been curbed by technological innovation. This is not surprising given that technological innovation in other areas of healthcare, although often associated with better outcomes, is rarely a source of cost savings.

There are certain mistaken beliefs regarding cost reduction in ICU: (i) that less cost will be incurred if ICU LOS is shortened, (ii) decrease in laboratory test will reduce the cost of care, and (iii) that restricting admissions of patients with futile care will save money. It is also important to realize that these cost savings may be at the ICU or hospital level.

The erroneous belief that decreasing LOS will decrease cost can be inferred from a cost-effectiveness analysis of antibiotic-coated catheters.³³ In this study, the authors assigned a cost of \$9,738 to a catheter-related bloodstream infection.³³ Patients with catheter-related infections have more risk-adjusted increased LOS.³⁴ The cost of a catheter-related infection may be calculated by multiplying the number of extra days spends in the hospital times and the hospital bed cost for a day in the ICU or ward. The randomized trials with antibiotic-coated catheters have not, however, convincingly showed decrease in ICU LOS.³⁵ Thus the money "saved" by reducing LOS is a different kind of money than money spent in buying the catheters.

In another example, if a drug is administered once daily than multiple times it is assumed to be less costly as the labor costs associated with administering medication is frequently more. On the other hand, if there is 15% less work to do,

one may not be able to hire 15% fewer nursing hours. This is because, if there is a need for 1:1 nursing care, the patient will continue to need this level of care regardless of whether the nurses are administering once-daily medication or not. Efficient use of nursing time may be achieved by changing nursing routine but this may not be reflected in a cost reduction. A reasonable criterion that needs to be considered as a cost saving measure is to see whether it will reduce the amount of staff that need to be hired or whether it will reduce acquisition costs for equipment or medication. If it will not then cost savings will not likely to happen.

Intensive care unit costs are maximum in the first few days of ICU stay, but most of the cost effective analyses erroneously assume a constant daily ICU cost.³⁶ Thus interventions which only reduce the last few ICU days will not have much impact on cost saving. This observation is rarely accounted for in the cost analysis.

Decreasing laboratory tests have been advocated as a cost-saving measure in ICU, which is justified on clinical grounds. False positives may lead to treatment of disease entities, which never existed. Charge-based analysis of ICU costing may give a false cost-saving impression in these situations. Saving cost by ordering one less blood gas when one has already purchased the blood gas analyzer and hired a technician may not be an effective strategy. The reduction in test ordering have to be of sufficient magnitude to decrease hiring less technician and purchasing less equipment to translate into a cost-saving maneuver. On the other hand, decreasing test order will lead to budgetary constraint on the laboratory, if staff numbers do not decrease proportionately. Point-of-care testing devices, which lead to less laboratory test ordering may be justified on clinical grounds but will not reduce overall hospital cost. Admitting patients with terminal illness to ICU may appear initially to be cost saving on face value, as they consume less ICU resources but this strategy may affect care that other patient with potential for survival might receive and may worsen overall health outcome.³⁷

ADHERING TO QUALITY INDICATORS AS TOOL FOR COST MINIMIZATION

A quality indicator is a screening tool to identify potential suboptimal clinical care.³⁸ Quality indicators provide a measure of quality-of-structure, process and outcome of care³⁹ and can serve as instruments to improve healthcare.⁴⁰ Structure indicators are related to the resources and means to be able to give treatment and care. Process refers to the activities related to treatment and care. Outcome is defined as changes in the state of health of a patient that can be attributed to an intervention or to the absence of an intervention. There are 120 identified quality indicators with their respective benchmarks. Adhering to these quality indicators significantly reduces the risks of iatrogenic and organizational adverse effects on patient outcome, significantly reduces the ICU LOS translating into cost

minimization. Of these 120 quality indicators, there are 20 bare minimum indicators, which are expected of every ICU to adhere to for patient safety, improve outcomes, and minimize cost. Seven of these twenty are most commonly used with an acronym "FAST HUG"⁴¹ indicating early feeding, adequate analgesia, adequate sedation, thromboprophylaxis, head-end elevation, stress ulcer prophylaxis, and glycemic control. The other 13 bare minimum indicators to be adhered to are:

1. Aspirin use for ischemic heart disease
2. Early vascular reperfusion for ST elevation myocardial infarction
3. Early surgery for evacuable intracranial hematoma
4. Intracranial pressure monitoring
5. Restrictive transfusion policy
6. Adverse events reporting
7. Adequate information provision to patient and families
8. Quality-of-life assessment
9. End-of-life care in ICU
10. Early goal directed therapy
11. Hand-washing policy
12. Twenty four hour intensivist cover
13. Facilitating organ donation.⁴²

The main goal is to use the indicators for internal comparison and internal use, by comparison within an ICU over time and by comparing with other ICU's on a national level. The indicator set currently identified can be used both to measure and to improve quality-of-care delivered in ICUs. Feedback on the indicators and comparison with other may stimulate improvement in quality for doctors, nurses, and other healthcare workers thereby improving the efficacy and cost-effectiveness of manpower. For comparison between ICUs, case mix plays a major role. For example, a method to make differences in mortality rate easier to interpret is to correct for severity of illness by using standardized mortality ratio. The set of indicators and their audit give a relatively quick view of the quality-of-care in individual ICUs.

USE OF GENERICS AS A TOOL FOR COST MINIMIZATION

Most studies related to cost minimization in healthcare are derived from United Kingdom and United States. The studies are mostly done with retrospective data and outpatient registries. There is considerable interest and debate concerning the place of generic substitution (switching from a brand to generic product); and on therapeutic substitution that is switching to a cheaper, but apparently equivalent, product, usually within the drug class.

The National Audit Office of United Kingdom published a follow-up report in May 2009 stating that substantial cost saving was achieved by substitution strategies in primary care with statins, proton pump inhibitors, drugs that affect the renin angiotensin system, and clopidogrel.⁴³ Some authorities have excluded the use of generics in certain areas

like modified or sustained release preparations, medicines with a narrow therapeutic window, vaccines, biosimilars, and controlled drugs.⁴⁴

Evidence for Generic Substitution

Generic prescribing is usually considered to be cost-effective.⁴⁵ There has been gradual increase in generic prescribing in some countries, e.g., in England, it increased from 30 to 88% over 5 years from mid 80s, which constituted 65% of all prescriptions because for the rest only a brand product was available as drugs were not "off patent" or because no generic alternative was available.⁴⁶ This is in stark contrast to the outpatient practice in United States, where branded product prescription is almost a rule even when a generic equivalent was available. This resulted in an estimated \$8.8 billion in excess expenditures per year in the United States.⁴⁷ This potentially may reflect physician and patient beliefs that brand name drugs are superior to their generic counterparts.⁴⁸ This difference among countries may be influenced by the local health, government, corporate, and insurance, policies. Generic manufacturers have to submit proof of bioequivalence to the regulatory authorities for approval. European regulations state that generic products must be shown to have bioavailability within the range of 80–125% of the reference product.

Studies Supporting the Bioequivalence of Generics to Branded Medicines

In one comparison of generic and branded salbutamol inhalers, 45% of patients claimed to have been able to detect some difference between their usual branded salbutamol inhaler and the generic one.⁴⁹ A survey in Germany found that 37% of patients expressed skepticism about generics because of their lower price and these patients were more likely to consider generic drugs inferior to branded products.⁵⁰

In a systemic review and meta-analysis, there was no evidence of superiority of brand name compared with generic drugs.⁵¹ In another systemic review of antiseizure medications indicated no difference in the odds of uncontrolled seizure for patients on generic medications compared with patients on brand-name medications.⁵²

The principle for substituting branded products for therapeutically equivalent alternatives is that of cost-minimization analysis, which is dependent on the notion of equal outcomes at reduced cost. The United Kingdom now has one of the highest rates of generic prescribing in the world (83% in the community in England in 2008). The main drivers for this in the National Health Scheme may be the historic belief in generic prescribing in medical schools and hospitals and that generic drugs are generally cheaper than their branded counterparts. Pharmacists play a large and important role in generic drug use and efforts to increase generic drug use directed at pharmacists should be

maintained.⁵³ Additional efforts to increase generic drug use likely should be targeted at prescribers.

CONCLUSION

From the studies reported, we could concur that significant cost minimization could be achieved by comprehensive approach encompassing short-cycle improvement, rationing, adherence to quality indicators and their benchmarks, and the use of generics. By applying this cost-minimization measure in all the nonlife-saving drugs used in ICU, there can be tremendous cost saving that could be achieved for the ICU patient. These cost-minimizing strategies need to be customized and individualized considering the fact that quality-of-care will suffer, if cost cutting is the sole determinant of care. A balanced approach is advocated and the cost-block methodology is the most efficient tool in these circumstances. Other administrative aspects like staffing pattern, reducing medical errors, ongoing audit, telemedicine, preventive care, etc. can also help in bringing down the total ICU costs.

REFERENCES

- Jacobs P, Noseworthy TW. National estimates of intensive care utilization and costs: Canada and the United States. *Crit Care Med*. 1990;18(11):1282-6.
- National Accounts Statistics 2001. McKinsey Analysis: 2001.
- Higgins AM, Harris AH. Health economics methods: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. *Crit Care Clin*. 2012;28(1):11-24.
- Talmor D, Shapiro N, Greenberg D, et al. When is critical care medicine cost-effective? A systematic review of the cost-effective literature. *Crit Care Med*. 2006;34(11):2738-47.
- Narang A, Kiran PS, Kumar P. Cost of neonatal intensive care in a tertiary care center. *Indian Pediatr*. 2005;42(10):989-97.
- Topeli A, Laghi F, Tobin MJ. Effect of closed unit policy and appointing an intensivist in a developing country. *Crit Care Med*. 2005;33(2):299-306.
- Parikh C, Karnad DR. Quality, cost and outcome of intensive care in a public hospital in Bombay, India. *Crit Care Med*. 1999;27(9):1754-9.
- Ghorra S, Reinert SE, Cioffi W, et al. Analysis of the effect of conversion from open to closed surgical intensive care unit. *Ann Surg*. 1999;229(2):163-7.
- Cole L, Bellomo R, Silvester W, et al. A prospective, multicenter study of the epidemiology, management and outcome of severe acute renal failure in a "closed" ICU system. *Am J Respir Crit Care Med*. 2000;162(1):191-6.
- Divatia JV, Baronia AK, Bhagwati A, et al. Critical care delivery in intensive care units in India: Defining the functions, roles and responsibilities of a consultant intensivist. *Indian J Crit Care Med*. 2006;10:53-63.
- Reynolds NH, Haupt MT, Thill-Baharozian MC, Carlson RW. Impact of critical care physician staffing with septic shock in a university hospital medical intensive care unit. *JAMA*. 1988;260:3446-50.
- Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. *Chest*. 1989;96(1):127-9.
- Manthous CA, Amoateng-Adjepong Y, al-Kharrat T, et al. Effects of medical consultant intensivist on patient care in a community teaching hospital. *Mayo Clin Proc*. 1997;72:391-9.
- Blunt MC, Burchett KR. Out-of-hours consultant cover and case-mix-adjusted mortality in intensive care. *Lancet*. 2000;356(9231):735-6.
- Abraham B, Raja JR, Mohan M. Activated protein C in sepsis: An Indian experience. *Crit Care*. 2005;9(Suppl 1):195.
- Fowler RA, Hill-Popper M, Stasinos J, et al. Cost-effectiveness of recombinant human activated protein C and the influence of severity of illness in the treatment of patients with severe sepsis. *J Crit Care*. 2003;18(3):181-91.
- Neilson AR, Burchardi H, Chinn C, et al. Cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in Germany. *J Crit Care*. 2003;18(4):217-27.
- Davies A, Ridley S, Hutton J, Chinn C, et al. Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. *Anaesthesia*. 2005;60(2):155-62.
- Riou Franca L, Launois R, Le Lay K, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis with multiple organ failure. *Int J Technol Assess Health Care*. 2006;22(1):101-8.
- Raja JR, Ramakrishnan N. ICU telemedicine: Promises and realities. *ICU Manage*. 2005;4:14.
- Marx WH, De Maenenon NL, Mooney KF, et al. Cost reduction and outcome improvement in the intensive care unit. *J Trauma*. 1999;46(4):625-30.
- Rubenfeld GD. Cost-effective critical care: cost containment and rationing. *Semin Respir Crit Care Med*. 2012;33(4):413-20.
- Asch DA, Ubel PA. Rationing by any other name. *N Engl J Med*. 1997;336(23):1668-71.
- Schroeder SA. Personal reflections on the high cost of American medical care: many causes but few politically sustainable solutions. *Arch Intern Med*. 2011;171(8):722-7.
- Mehlman MJ. The legal implications of health care cost containment: a symposium: health care cost containment and medical technology: a critique of waste theory. *Case Western Reserve Law Rev*. 1986;36:778-877.
- Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-17.
- Brook RH, Chassin MR, Fink A, et al. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care*. 1986;2(1):53-63.
- Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341(11):785-92.
- Kahneman D, Slovic P, Tversky A. *Judgment under Uncertainty: Heuristics and Biases*. Cambridge; New York: Cambridge University Press; 1987.
- Jonsen AR. Bentham in a box: technology assessment and health care allocation. *Law Med Health Care*. 1986;14(3-4):172-4.
- Alderson P, Schierhout G, Roberts I, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2000;(2):CD000567.
- Morgan A, Daly C, Murawski BJ. Dollar and human costs of intensive care. *J Surg Res*. 1973;14(5):441-8.
- Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA*. 1999;282(6):554-60.
- Digiovine B, Chenoweth C, Watts C, et al. The attributable mortality and costs of primary nosocomial blood stream infections in the intensive care unit. *Am J Respir Crit Care Med*. 1999;160(3):976-81.
- Darouiche RO, Raad II, Heard SO, et al. Catheter Study Group. A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med*. 1999;340(1):1-8.
- Rapoport J, Teres D, Zhao Y, et al. Length of stay data as a guide to hospital economic performance for ICU patients. *Med Care*. 2003;41(3):386-97.
- Luce JM, Rubenfeld GD. Can health care costs be reduced by limiting intensive care at the end of life? *Am J Respir Crit Care Med*. 2002;165(6):750-4.
- AHRQ quality indicators. Guide to patient safety indicators. AHRQ. 2003; 2(1):1-65.
- Skews G, Meehan T, Hunt G, et al. Development and validation of clinical indicators for mental health nursing practice. *Aust N Z J Mental Health Nurs*. 2000;9(1):11-8.

40. Donabedian A (Ed). *An Introduction to Quality Assurance in Health Care*. 1st ed. New York: Oxford University Press; 2003.
41. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med*. 2005;33(6):1225-9.
42. Martin M, Saura R, Cabre L, et al. Quality indicators in critically ill patients. *Crit Care*. 2006;10(Suppl 1):395.
43. National Audit Office (2007). Prescribing costs in primary care. [online] Available from: http://www.nao.org.uk/publications/0607/prescribing_costs_in_primary_c.aspx. [Accessed September, 2016].
44. The Association of the British Pharmaceutical Industry (2010). Generic substitution: patient safety comes first. [online] Available from: <http://www.abpi.org.uk/media-centre/newsreleases/2010/Pages/050110.aspx>. [Accessed September, 2016].
45. Duerden MG (2006). Making sense of drug pricing. WeMeReC Online resources. [online] Available from: <http://www.wemerec.org/Document/notes/MedicinesPricing.pdf>. [Accessed September, 2016].
46. Department of Health (2010). The proposals to implement 'generic substitution' in primary care, further to the Pharmaceutical Price Regulation Scheme (PPRS) 2009. Consultation document 2010. [online] Available from: http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_110517. [Accessed September, 2016].
47. Haas JS, Phillips KA, Gerstenberger EP, et al. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997-2000. *Ann Intern Med*. 2005;142(11):891-7.
48. Banahan BF 3rd, Kolassa EM. A physician survey on generic drugs and substitution of critical dose medications. *Arch Intern Med*. 1997;157(18):2080-8.
49. Williamson LJ, Reid A, Monel RD, et al. Generic inhaled salbutamol versus branded salbutamol. A randomized double-blind study. *Postgrad Med J*. 1997;73(857):156-8.
50. Himmel W, Simmenroth-Nayda A, Neibling W, et al. What do primary care patients think about generic drugs? *Int J Clin Pharmacol Ther*. 2005;43(10):472-9.
51. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardio-vascular disease: a systematic review and meta-analysis. *JAMA*. 2008;300(21):2514-26.
52. Kesselheim AS, Stedman MR, Bubrick ej, et al. Seizure outcomes following the use of generic versus brand-name anti-epileptic drugs: a systematic review and meta-analysis. *Drugs*. 2010;70(5):605-21.
53. Mott DA, Cline RR. Exploring generic drug use behaviour: the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution. *Med Care*. 2002;40(8):662-74.

Methods of Cost-effectiveness Analysis

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INTRODUCTION

Healthcare costs are constantly increasing due to rising cost of medicines, appliances, use of more and more advanced and complex technology in healthcare delivery and rising aspirations of patients for a complete or near complete recovery. Since private sector caters to most of the serious patients at least in India and there is a rise of medical litigation with its cascading effects on diagnostic tests and therapeutic interventions, this becomes an important issue for the medical fraternity to address. In critical care, the technology required to treat, human resources required to care, and the interventions required to support the failing organs for a varying period of time need more resources than most other disciplines in healthcare. In the United States, critical care beds account for 5–10% of all acute care beds; but accounts for 20–34% of acute care resources which amounted to 1% of gross domestic product (GDP) i.e., \$67 billion (in 1994).¹ Healthcare costs at that stage was accounting for 14% of GDP which was predicted to grow at 2% every 3 years. In India, government spending in healthcare is still <3% of GDP and therefore large section of the society falls back on private sector which provides high-end care at a very high-cost considering the average annual income of less than \$1,500 for an Indian. Most of this cost comes from insurance companies and corporate houses (for their employees), but majority of patients are still to pay in cash from their earnings. It is often seen that patients have to sell their assets to meet the healthcare costs, particularly intensive care costs. It is, therefore, necessary to understand the economics of critical care before one could try to evaluate its effectiveness and contain it.

DEFINITIONS

Cost and Charge

Cost and charge are not the same. Cost is the true expenditure, while charge is what the hospital would like to reimburse

from the patient. Charge includes cost plus profit that a healthcare provider would like to make. Cost can be derived from charges based on hospital-specific “cost to charge” ratios, if available. For cost-effectiveness considerations, cost is taken. Cost can be “direct and indirect” (and intangible) and “fixed and variable”. Direct costs are labor and goods utilized in care delivery and indirect costs are due to productivity loss because of illness. Intangible cost is due to pain and suffering associated with the intervention. Fixed costs are the costs which remain the same regardless of the output and include the cost of man, machine, and maintenance. Variable cost is the cost of medicines and consumables and the cost required to temporarily increase for a temporary surge of patients in intensive care unit (ICU), e.g., hiring more number of nurses.

Cost-effectiveness

Cost is all expenditure that is made for a given set of alternatives and is measured in terms of money and effectiveness is benefit expressed in terms of outcome i.e., number of survivors, number of years of life gained or quality-adjusted life years (QALYs). A cost-effective ratio (CER) is calculated for each alternative and compared. Incremental cost-effectiveness ratio is defined as incremental cost of treatment being evaluated compared to standard treatment or incremental benefit compared to standard treatment.

Cost-benefit

Cost-benefit is usually meant as cost-effectiveness except that cost-benefit is calculated in monetary terms thus not applied to clinical outcomes.

Cost-utility

Cost-utility is a subset of cost-effectiveness in which it attempts to incorporate mortality and morbidity in a single effectiveness measure such as QALYs.

Cost-minimization

Cost-minimization simply measures the cost without taking effectiveness into consideration.

Cost-consequence

An analysis where cost and consequences are noted separately allowing the end user to choose the costs and consequences relevant to their situation.

Cost-effectiveness Analysis

Cost-effectiveness analysis (CEA) compares the expected benefits of an intervention with its net costs.

Cost-utility Analysis

Cost-utility analysis (CUA) is a type of CEA that uses cost and effectiveness of therapies using QALYs, e.g., the quality (utility) of a health state dependent on a ventilator is lower than independent of a ventilator.

Cost-utility analysis is calculated in two ways: either by "top-down" or "bottom-up" method.²

1. Top-down method: It takes the overall cost of care in ICU and divides it by total number of patient-days of care to get the average cost per day. To this, some estimate of overheads is added for calculating the average bill per day to the patient. This calculation is usually easy but not necessarily accurate
2. Bottom-up method: This approach takes into account the cost of discrete items that are used and the cost of many hours spent on the patient. Even with these details, assigning a financial value to these costs is not easy as cost of air conditioning, maintenance, infection control practices, waste disposal, etc. are not factored into this calculation. So not surprisingly, top-down and bottom-up approaches give quite different cost estimates.

Top-down approach is generally adopted by most researchers. The researchers of "the cost-effective study of antimicrobial coated catheters" used this approach to calculate each day's ICU cost in 1999 as \$1,152 which was roughly three times the average hospital day's cost.³ A simple calculation can be made from the increase in ICU stay by 5 days due to catheter-related bloodstream infection (CRBSI) will increase the bill by \$5,760 ($1,152 \times 5$). Conversely, if the average length of ICU stay (ALOS) at the end of the year is reduced by 0.5 day and the total number of patients treated is 500, then the money saved (which goes to the bills) for all of them are \$288,000 ($500 \times 0.5 \times 1,152$). In addition to the savings for the patients, the hospital can also treat more number of patients ($\text{ICU patient days gained} / \text{ALOS} = \text{no. of pts who could be accommodated}$) with the same establishment and infrastructural maintenance cost. This simple arithmetic calculation, however, may not hold true in a real life situation for the following reasons:

- Variable costs (pharmacy, investigations, consumables, etc.) per day toward last days or hours of ICU stay are much less compared to first few days of admission.⁴ So saving these last few days in ICU will not deduct much from the expenses
- Reducing ICU stay can even increase the hospital cost as the new patient will require more therapies and investigations in first few days even though it creates more access for the needy patient
- If an intervention such as early surgery, reduces ICU stay, the ICU cost reduction will be less even though that needs to be done.

Turunen et al. studied the economic benefits of dexmedetomidine sedation versus midazolam and propofol sedation in reducing the days of mechanical ventilation.⁵ There were criticisms for these trials; but certain findings are worth noting. Firstly, reduction of a day on mechanical ventilation would cost 33% less compared to a day on mechanical ventilation and secondly, they did sensitivity analysis to find out if costing assumptions changed the results. Though dexmedetomidine was cost-effective in all scenarios, the savings were small compared to propofol and that has to be interpreted against dexmedetomidine's disadvantages of bradycardia and hypotension.

COST-MINIMIZATION VERSUS COST-EFFECTIVENESS

Cost-minimization assumes that the considered treatment or technique does not affect the "nonmortality" outcomes adversely. The protagonists of this approach generally take some morbidity parameters such as "days of mechanical ventilation" as a parameter of weaning and ALOS. While the former parameter is reduced in a case of "successful weaning", it is also reduced in a case of "dying early". Similarly, ALOS could come down if patient spends 1 day less in ICU and it can also come down if relatives take away their patient because of so many reasons. So cost-minimization is now replaced with cost-effectiveness which positions cost against safety and efficiency.⁶

In a study of cost-effectiveness in critical care in the United Kingdom, evaluation of trends in inputs (beds, costs), processes (discharge practices, length of stay, transfers between units and readmissions) and outcomes (unit and hospital mortality) were compared with adjustments for case mix between 1998 and 2000 with last quarters of 2000–06.⁷ Differences in annual cost and QALYs were used to calculate net monetary benefits (one QALY gain was taken as equivalent to £20,000, i.e., \$33,170). There were 96 critical care units and 349,817 admissions. In 6 years, the risk of unit mortality adjusted for case mix reduced by 11.3% and hospital mortality by 13.4% compared to steady state in 3 preceding years and there was substantial reduction in unplanned night discharges and transfers between units with the mean annual benefits increasing significantly signaling the changes were cost-effective. In another study in the United Kingdom, Ridly

and Morris reported that adult intensive care represents good value for money.⁸

COST-EFFECTIVENESS AS A PART OF HEALTH TECHNOLOGY ASSESSMENT

Every new technology used in healthcare (in case of ICU, includes ventilators, monitors, drug delivery systems, catheters, representing fixed and variable costs) goes through systematic review, meta-analysis, clinical trials, epidemiology, and economic evaluation.⁹ Health technology assessment (HTA) is undertaken by national agencies such as Agency for Healthcare Research and Quality in the United States and National Institute for Health and Care Excellence (NICE) in the United Kingdom. No such organization has been established in India, though the Indian Society of Pharmacoeconomics and Outcomes Research (ISPOR) have taken some initiative to do this work. National Health Systems and Resource Centre (NHSRC) under the National Rural Health Mission of Government of India (NRHM) was established in 2007 with an intention of improving health outcomes by system improvements, facilitating reforms, and sharing information amongst the various stakeholders. The first compendium of HTA was launched at the fourth International HTA fellowship in Chennai in August 2014. This was an outcome of the fellowship program organized by the NHSRC and WHO India during 2012 and 2013. Already more than 200 candidates have qualified for the fellowship in HTA. This is a critical step towards establishing an organization for a comprehensive cost-effective healthcare development plan in India.

Health Outcomes

Effectiveness is assessed by health outcomes which are multidimensional parameters reduced to single index using health utilities, e.g., QALYs, i.e., healthy years equivalents where a common unit is determined by using a multidimensional measure of health status, which is weighted according to individuals' preferences.¹⁰ So, QALY is a measure of length of life, expressed in life years, weighted by the health related quality of life as valued by a preference-based score. The QALYs aggregate the total health improvement for a group of individuals in one single measure. "Utility" is the value of a health outcome that can be received by the patient and his relatives. Feeney and Torrance demonstrated that utility measurement could be used to assess "quality of life" outcomes. They concluded that "when study specific utilities are carefully developed and deployed, they are reliable, valid and responsive".¹¹ Once utilities are estimated, QALYs are compared with costs in the form of an incremental cost-effective ratio i.e., CER (refers to the ratio of incremental cost of new therapy compared with standard therapy to

incremental health gain of a new therapy also compared with standard therapy) and comparisons between various interventions and management protocols can be made using cost per QALY gained.¹² Strategies that cost less compared to the threshold per desired health outcome (e.g., cost per survival, measured in QALY) are considered cost-effective. The threshold to pay for desired health outcome is traditionally put at \$50,000 per QALY.^{13,14} Economic evaluations must have a perspective (refers to "who is paying in the analysis; the hospital or patient or insurance companies or employer") and a timeline (the time period over which cost and outcome are analyzed). A cost-effective analysis (CEA) in a teaching hospital in South India evaluated the clinical and economic results of salmeterol or fluticasone, formoterol or budesonide, and formoterol or fluticasone in patients with severe and very severe chronic obstructive pulmonary disease (COPD). They showed that combined use of corticosteroid inhalations and bronchodilators in COPD has the potential to improve clinical outcomes compared to current practice without increasing the costs.¹⁵

Cost

Cost is a function of resource quantities and their unit costs. Healthcare cost is calculated from direct medical and nonmedical costs, patients' cost, and indirect production losses by the patient due to illness and death. Optimal use of a technology or strategy of management would be achieved when marginal cost (cost incurred to provide an additional service, calculated from labor cost, consumable cost, and overhead cost) is equal to marginal benefit also known as marginal utility (gain in service from a decrease in consumption of that service). In economics, utility is the satisfaction or benefit derived by consuming a product or service and marginal utility of a service is the change in utility from increase or decrease in the consumption of that service. As cost estimates and income levels vary in different populations, a CEA in one population would not be applicable in another unless it is a similar population.

Utility

Utility, a measure which ranges from 0 for death to 1 for perfect health, reflects patient's preference for a given health state which, when multiplied with number of years he/she survives in that state, generates QALYs. Cost-utility analysis is a type of CEA that examines the cost and effectiveness of therapies in terms of life years (QALYs) gained.

Health Economic Analysis

Cost and outcomes (including CER) could be taken as parameters in studies.^{16,17}

Methods for Cost-effectiveness Analysis

The methods for CEA adopted are:

- Building decision trees from the available literature which informs a computer-based model that is designed to predict outcomes and cost inputs are derived from surveying hospitals or patients accessing national data base or from the published literature
- Incorporating an economic evaluation into a randomized control trial.¹⁸⁻²⁰

A new therapy has to be proved as effective and then cost-effective before being introduced into practice. In certain countries like Canada and the United Kingdom, new therapies may not be approved unless they are cost-effective. The conventional ventilation or extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure (CESAR) was a trial designed with a parallel cost-effectiveness as an outcome.²¹ The authors found out that transporting a patient of adult respiratory distress syndrome (ARDS) to a specialized center for ECMO was associated with a 16.2% absolute risk reduction of death and disability at 6 months. They also performed a CUA and found the cost of transport to the center with ECMO facility was £19,252 per QALY gained (at 2005 rates).

In a meta-analysis of CEAs, 19 studies were identified between 1993 and 2003 with 48 CER pertaining to severe sepsis, acute respiratory failure, and general intensive care interventions.²² The cost-effectiveness of activated protein C in sepsis was analyzed as:

- Cost per life year saved was \$12,570–33,100
- Cost per QALY gained was \$20,047–48,800.

It was a cost-effective (less than \$50,000 per QALY gained) proposition but when it was stratified by risk, it demonstrated otherwise in that with Acute Physiology and Chronic Health Evaluation (APACHE II) <25, the incremental CER reached \$575,054/year saved and \$958,423/QALY gained compared with \$19,723 and 32,872, respectively, in higher risk group (APACHE II >25). Similarly, the cost-effectiveness of mechanical ventilation in respiratory failure ranged between \$26,283/QALY and 174,200/QALY depending on the risk factors. While in lower risk patients, mechanical ventilation was cost-effective, in higher risk (>40 years, stroke, human immunodeficiency virus infection, pneumocystis pneumonia) patients, mechanical ventilation was associated with incremental CER of more than \$100,000/QALY gained. Likewise, admissions to ICUs, when studied, the CEA ratios ranged from \$168/QALY saved in asthma to \$189,339/QALY saved in hematological malignancies. At the time of this review, there seemed to be a general consensus in the US treatments with a CER of United States \$50,000–100,000 was acceptable to the society. This figure could vary in other countries depending on the socioeconomic status of their population.

Difficulties in Conducting Cost-effectiveness Analysis

In order to study the cost-effectiveness of an ICU intervention, first it has to be ascertained that the intervention is effective and then its cost-effectiveness has to be studied. Generally, it is observed that most studies on CEAs take into account the hospital expenses (fixed and variable); but there are many other costs which also should be taken into account. Those costs are rehabilitation costs, home care costs, hospice costs, relative's personal out-of-pocket costs, and opportunity costs (cost of time spent for training physicians, nurses, and technicians and loss of earnings due to time spent by the family members in attending family meetings). With no accounting of these costs, a new intervention in ICU might prove to be effective but not cost-effective in terms of QALYs and quality of life gained. There are, as described earlier, two approaches for CEA which are (i) top-down and (ii) bottom-up. A top-down approach takes the total expenditure and divides it by the number of patients to get the mean cost per patient and a bottom-up approach tabulates painstakingly each component of expenditure for the patient to find the total expenditure for that patient at the end of his or her ICU stay. The first method is "attributable costing" and the second method is called "microcosting". Both approaches have got their pitfalls. If one takes the average cost in to consideration, it is not a true representative of the daily cost for an ICU admission; the initial 2 or 3 days are too expensive compared to the later days because of the instability of the patient requiring maximum investigations and interventions in the former. Therefore, reducing the ICU stay does not represent a true cost-effective parameter.^{23,24}

In order to do a CUA, one needs to measure the quantity and quality of life over long time periods (not just ICU or even 28 days' hospital mortality). Utility is expressed as 0 for death to 1 for perfect health (patients prefer a particular value within this range for a given health state) multiplied by the number of years he or she survives in that health state to give QALYs among the survivors of critical illness.^{25,26} Researchers have used surveys on patients using short form 36-dimensions or EuroQol 5-dimensions which ensures completeness of response and follow-up. These studies showed that survivors of critical illness have decreased survival, decreased quality of life, increased costs, and increased use of healthcare services compared to the normal population of that age group.

Perspective

Central to any cost analysis is the idea of perspective. For example, cost to avoid a ventilator-associated pneumonia (VAP) is important for the hospital; therefore, it is an outcome important to hospital's perspective whereas QALY

represents a perspective important to patient, community, and agencies providing healthcare funding. In a study by Angus et al. with (activated) drotrecogin alfa in severe sepsis, the investigators, while examining incremental healthcare costs with one death averted in 28 days, found that it was \$160,000 per life saved and \$48,000 per QALY; this improved to \$27,000 when risk of death increased and worsened to \$100,000 per QALY if the subject lived for <5 years.²⁷ While cost per death averted was calculated as per actual, the cost-utility ratio was calculated based on a modeling exercise.

Incremental Cost-effectiveness Ratio

Cost-effectiveness analysis could be utilized in comparative analysis of two interventions for the same condition. Cost effective ratio is the ratio of differences in cost to differences in effectiveness of the two therapies being compared. The lower the result, the better the cost-effectiveness profile. Shorr's study, while comparing the cost-effectiveness of linezolid versus vancomycin in methicillin resistant *Staphylococcus aureus* induced VAP, calculated that incremental cost per survivor, per life year saved, and per QALY was \$67,000, 22,000, and 30,000, respectively.²⁸ In another study, cost-effectiveness of micafungin was compared with fluconazole for empirical treatment of candidemia in ICU; the cost per QALY was \$35,000 (26–50,000) and in a worst case scenario of multivariate analysis (all of the inputs are varied at the same time), where all the inputs were skewed in favor of fluconazole, the CER was \$72,000 per QALY.²⁹

Inflation Adjustment and Discounting

Cost-effectiveness calculations must do adjustments for inflation as the inputs for a model may represent the costs of the past and medical cost inflation is rapid. Likewise, one has to discount future costs (life time healthcare costs) and effectiveness (QALYs) estimates in both the numerator and denominator. The recommended annual base discount rate is taken as 3% (0–7%).³⁰

CONCLUSION

Methods of cost-effectiveness in ICU are many and complicated. Getting the cost as per actual expenditure through bottom-up approach or by dividing the total expenditure by number of patients through top-down approach is not easy for a comprehensive cost calculation as many other costs, such as rehabilitation cost, home and hospice cost and opportunity cost are not generally included. Usual ICU outcomes such as ICU mortality, ALOS, average ventilator days, and 28 days hospital mortality are unsuitable as cost-effectiveness parameters. Quality-adjusted life year (QALY) and CER are better parameters for CEA in ICU. Cost-effectiveness analysis in ICU in India is still in its infancy. Some effort has been made by NBSRC under the

auspices of NRHM. Setting our own CER for the ICU will go a long way in deciding the interventions in the ICU for our population. At present, in absence of a cost-effective outcome parameter such as QALY for our population, we will always be at a disadvantage to assess whether our ICUs and our interventions are truly cost-effective.

REFERENCES

- Chalfin DB, Cohen IL, Lambrinos J. The economics and cost effectiveness of critical care medicine. *Intensive Care Med.* 1995;21(11):952-61.
- Wilcox ME, Rubinfeld GD. Is critical care ready for an economic surrogate end point? *Critical Care.* 2015;19:248.
- Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA.* 1999;282(6):554-60.
- Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med.* 2005;33(6):1266-71.
- Turunen H, Jakob SM, Ruokonen E, et al. Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation. *Crit Care.* 2015;19:67.
- Dakin H, Wordsworth S. Cost-minimization analysis versus cost-effectiveness analysis, revisited. *Health Econ.* 2013;22(1):22-34.
- Hutchings A, Durand MA, Grieve R, et al. Evaluation of modernization of adult critical care services in England: time series and cost effectiveness analysis. *BMJ.* 2009;339: b4353.
- Ridley S, Morris S. Cost effectiveness in adult intensive care in the UK. *Anaesthesia.* 2007;62(6):547-54.
- Maynard A, Macdaid D. Evaluating health interventions: exploiting the potential. *Health Policy.* 2003;63(2):215-26.
- Slothuus U. Economic evaluation theory, methods & application. *Health Economics Papers.* 2005:5.
- Feeney DH, Torrance GW. Incorporating utility-based quality-of-life assessment measures in clinical trials: two examples. *Med Care.* 1989;27(3):S197-204.
- Lorgelly PK, Lawson KD, Fenwick EAL, et al. Outcome measurement in economic evaluations of public health Interventions: a role for the capability approach? *Int J Environ Res Public Health.* 2010;7(5):2274-89.
- Lee CP, Chertow GM, Zenios SA. An empiric estimate of value of Life: updating the renal dialysis cost-effectiveness standard. *Value Health.* 2009;12(1):80-7.
- World Health Organisation (2016). Choosing interventions that are cost-effective (WHO-CHOICE) [online]. Available from: www.who.int/choice/costs/CER_levels/en/ [Accessed September 2016].
- Altai M, Zubedi AM, Nazneen F, et al. Cost-effective analysis of three different combination of inhalers for severe and very severe chronic obstructive pulmonary disease patients at a tertiary care teaching hospital in South India. *Perspect Clin Res.* 2015;6(3):150-8.
- Understanding cost and cost-effectiveness in critical care: report from 2nd American Thoracic Society workshop on outcomes research. *Am J Resp Crit Care Med.* 2002;165(4):540-50.
- Coughlin MT, Angus DC. Economic evaluation of new therapies in critical illness. *Crit Care Med.* 2003;31(1):S7-16.
- Peek GJ, Elbourne D, Mugford M, et al. Randomised control trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess.* 2010;14(35):1-46.
- Stevens K, McCabe C, Jones C, et al. The incremental cost effectiveness of withdrawing pulmonary artery catheters from routine use in critical care. *Appl Health Econ Health Policy.* 2005;4(4):257-64.
- Harvey S, Harrison DA, Singer M, et al. Assessment of clinical use of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomized controlled trial. *Lancet.* 2005;366(9484):472-7.
- Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economics of conventional ventilator support versus

- extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). A multicentre randomized controlled trial. *Lancet*. 2009;374(9698):1351-63.
22. Daniel T, Nathan S, Dan G, et al. When is Critical Care Medicine cost-effective? A systematic review of cost-effective literature. *Crit Care Med*. 2006;34(11):2738-47.
23. Kahn JM, Rubenfeld GD, Rohrbach J, et al. Cost savings attributable to intensive care unit length of stay for mechanically ventilated patients. *Med Care*. 2008;46(12):1226-33.
24. Al MJ, Hakkaart L, Tan SS, et al. Cost-consequence analysis of remifentanyl-based analgo-sedation vs. conventional analgesia and sedation for patients on mechanical ventilation in The Netherlands. *Crit Care*. 2010;14(6):R195.
25. Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. *Crit Care*. 2010;14(1):R6.
26. Herridge MS, Tansey CM, Matte A, et al. Functional disability five years after acute respiratory distress syndrome. *New Eng J Med*. 2011;364(14):1293-304.
27. Angus DC, Linde-Zwirble WT, Clermet G, Ball DE, Basson BR, Ely EW, et al. PROWESS investigators. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med*. 2003;31(1):1-11.
28. Shorr AF, Susla GM, Koller MH. Linezolid for treatment of ventilator associated pneumonia: a cost-effective alternative to vancomycin. *Crit Care Med*. 2004;32(1):137-43.
29. Zilberberg MD, Kothari S, Shorr AF. Cost-effectiveness of micafungin as an alternative to fluconazole empiric treatment of suspected ICU-acquired candidemia among patients with sepsis: a model simulation. *Crit Care*. 2009;13(3):R94.
30. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA*. 1996;276(15):1253-8.

Intensive Care Unit Costs and Resource-limited Settings

JV Peter

INTRODUCTION

Over the last few decades, improvements in public health services and better delivery of primary healthcare have improved sanitation, immunization, maternal care, and family planning that have translated to reduction in birth rate, infant mortality rate, maternal mortality rate, as well improvement in life expectancy in India.^{1,2} National health programs focusing initially on infectious diseases such as malaria and tuberculosis and subsequently on noncommunicable diseases such as diabetes and cancer have helped to improve the quality and quantity of life in our country. Unfortunately, till recently, not much attention has been paid to critical care services in India. This is exemplified by the fact that there are only about 70,000 intensive care unit (ICU) beds in India for a population of over 1 billion;³ a large proportion of these beds (estimated to be around 90%) are in the private sector where patients have to pay for the cost of treatment. It is estimated that one episode of hospitalization accounts for about 58% of the per capita expenditure that pushes about 2.2% of families below the poverty line.³ Recent reports have suggested that the out of pocket expenses in India for health have increased from an already alarming 60% in 2012 to 70% in 2015.⁴ In light of these factors, it is important not only to look at ways by which the capacity of ICU beds in the country is increased, but also to explore mechanisms by which the cost of the services can be made affordable to the majority.

INTENSIVE CARE RESOURCES

An important impediment for capacity planning and building in resource-limited settings has been the limited data on the availability of critical care resource, its utilization, and outcomes of patients treated for critical illness.¹ Although the 70,000 intensive care beds in the country would probably translate to around 0.5–0.6 beds per 100,000 population, information on the nature of such beds (distribution in

terms of the level of the ICU beds as level I, II, or III) and the location of beds (rural, semiurban, and urban) is lacking. The deficiency in ICU beds in our country is in stark contrast to other countries where the number of ICU beds per 100,000 population is 20 beds the United States, 3.5 in the United Kingdom, and 2.5 in Sri Lanka.⁵ Further, in the hospital setting, it is recommended that about 10% of the beds are earmarked as critical care beds. In the United States, 13.4% of the beds are allocated for critical care,⁶ while in Cape Town in South Africa it is about 6.6%.⁷ These estimates are not available for India, although it is likely that very few hospitals, except probably the corporate hospitals, can afford allocation of 10% of beds for critical care. This is probably because of the perception that not only is critical care expensive, it is resource intense and the outcome of patients admitted with critical illness is poorer when compared with outcome from other disease processes. It may also be argued that allocation of additional resources to critical care may potentially steal away resources from other more reversible disease processes and surgical problems.

Another factor that may be contributing to the slow pace of development of critical care in India, particularly in the public sector, is the quantum of allocation of the gross domestic product (GDP) for health. The World Bank estimated that the GDP allocation for health in India in 2014 was about 4.7% compared with 5.5% in China, 9.1% in United Kingdom, and 17.1% in the United States.⁸ Current estimates suggest that in 2016, the allocation for health was a meager 3%.⁹ To compound this, India loses about 6% of its annual GDP to preventable illnesses and premature deaths,⁴ seriously compromising on the health and productivity of the nation. With several competing needs for the GDP allocation to health for primary, secondary, and tertiary healthcare in the country, it is not surprising that allocation for critical care services is not a priority in the public sector. Thus it is imperative that the critical care scenario in India is carefully studied. Three aspects merit discussion: (i) mitigation of risk of critical illness, (ii) provision of appropriate/adequate

intensive care services, and (iii) optimal utilization of the available resources.

Mitigation of Risk of Critical Illness

Several measures need to be considered in order to mitigate the risk of critical illness in the community (Flowchart 1). One of the major factors that strains critical care services in India is the continued burden of infectious diseases. Sepsis and septic shock due to tropical diseases like malaria, scrub typhus, and dengue continue to plague our nation, in addition to other infections such as urosepsis, pneumonia, and central nervous system infections. Mortality due to sepsis as a whole is considerably higher in sub-Saharan Africa (56%) and South Asia (29%) than the 6% in high-income countries.⁵ Aggressive public health measures to control the vectors that transmit these infections would translate to a reduction in the burden of critical illness.

In those who develop illness, easy, and rapid access to healthcare is crucial. The time lag to seek medical help is often long, particularly in remote areas of the country, resulting in significant derangement of physiology that makes it more difficult and longer to reverse, placing further demands on an already stretched system. Time delays to some extent have been addressed by the provision of 108 ambulance services in the country that are generally able to reach the patient quickly and transport to the nearest healthcare facility within 15–20 minutes.¹⁰ However, at times, when the patient does reach a base hospital, the first responder may not be available and even if one is available, the healthcare worker (e.g., nurse or doctor) may not be adequately equipped or trained to manage critical illness. Appropriate facilities may not always be available at the first point of care, including basic equipment for monitoring, treatment, and diagnosis.^{1,2} Laboratory services may be limited by manpower or lack of proper maintenance of equipments. The supplies of essential medications may be erratic and radiology services may be unavailable.

Provision of Adequate Resources

Recently, there have been numerous publications that have emphasized the need for building intensive care capacity in low-income countries.^{11–13} An ICU that is set up rationally would prioritize basic and inexpensive therapies and fit into

a coordinated service that benefits all critically ill patients.¹⁴ The exact nature, size, and structure of the ICU would depend on the case-mix that is prevalent in that area, the financial and human resource that can be accessed, as well as the community needs.¹⁴ Focus on simple therapies such as close monitoring, appropriate and adequate fluid resuscitation, oxygen therapy, pain management, and monitoring of urine output are likely to make an impact on the outcome of patients,¹⁴ particularly in resource-limited settings.

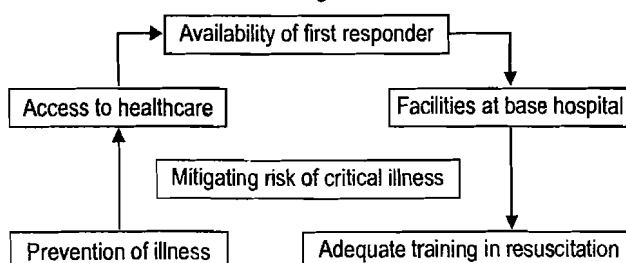
Three stakeholders are involved in the provision of healthcare in India, namely, the public sector hospitals, the not-for-profit charitable organizations and the for-profit private sector hospitals. Capacity building in all these three sectors is important to increase the number of beds available to treat critical illness. The mandate by the government to allocate at least 10% of the beds in the private sector hospitals as hospital free beds does benefit a small subset of patients who cannot afford expensive treatment. However, there is still be a huge shortfall in the number of beds needed to meet the demand for critical care and hence other principles of resource allocation may need to be considered.

Optimal Utilization of Resources

Healthcare in India is a fundamental right enshrined in the Constitution of India. This means that the principle of equity needs to be applied, in that every individual has equal right to access to healthcare including critical care services.¹⁵ However, in reality, due to the gross demand-supply mismatch, the principle of utility which is generally recommended to be applied in situations of mass disaster or pandemics may need to be considered. The principle of utility suggests that resources should be used to provide the maximum possible health benefits, often understood as “saving most lives.”¹⁵ However, it must be emphasized that an appropriate balance needs to be struck and allocation of resources should be done in an open and transparent process taking into consideration local circumstances and cultural values.¹⁵

A recent study from India looked at cost utility in intensive care patients as a scientific way of allocation of intensive care resources.¹⁶ In this study, utility was scored by the ICU doctor as well as the medical doctor as a score between 0 and 1 with incremental scores of 0.1. A utility score of 1 was given, if the patient was likely to have perfect health in terms of quality of life as well as preserved longevity, in terms of quantity of life. A score of 0 was assigned to death. Scores between 0 and 1 represented varying severity of illness as well as the perceived quality of life following recovery from critical illness. In the study, utility score of less than or equal to 0.3 on day 2 was associated with a survival of 8.3%, while a score of more than or equal to 0.8 on day 5 was associated with a survival of 94.6%. The authors argued that a patient with a low-utility score on day 2 should be given a “short” trial of ICU care for

FLOWCHART 1 Measures to mitigate the risk of critical illness



a period of 2–3 days to ascertain response to therapy and then a decision should be made on continuation of ongoing aggressive treatment.¹⁶ This philosophy of an “ICU trial” is not new since policies for the treatment of cancer patients needing intensive care in the United States evolved from “just say no”¹⁷ in 1898 to “consider saying yes”¹⁸ to an “ICU trial”¹⁹ in the last decade. On the other end of the spectrum, those with a high-utility score on day 5 had a high probability of survival and hence these patients could be considered for transition from a high-intensity area to a lower intensity area, particularly, if the requirement for organ support was minimal. The application of scientific ways of assessing prognosis and allocating resources to tiered levels of ICU may help to optimize the utilization of intensive care services.²⁰ However, this requires further study and validation.

Resource Pooling

Resource pooling, a concept well accepted in management circles, is another method of ensuring optimal utilization of healthcare resource. There has been recent interest in resource pooling in the health sector. Centralized functioning may reduce manpower and equipment requirements. On the other hand, services that are organized around patient groups may be able to provide focused, quality care.^{21,22} Critical care units in developed countries are predominantly mixed medical-surgical units. However, in India, critical care units have often developed around specific specialties. Thus, the medical critical care units are run by the physicians, the surgical critical care units by the anesthetists, the cardiothoracic critical care units by the cardiothoracic surgeons, and so on. Decentralizing of critical care as medical, surgical, neuro, or cardiac critical care, while having its merits of focused, high-quality care, often tends to result in duplication of services (e.g., point of care testing, need for ventilators, pumps, etc.), and need for increased number of trained manpower (nursing, medical, and technical) to service each of these areas. Resource pooling of nurses, trained in basic and advanced life support, ventilation, and hemodynamics, is already happening in developed countries where nurses are allocated on that specific shift to areas that require them. Such pooling will optimize manpower resources. The provision of larger mixed medical-surgical ICUs separated out as pods for ease of function, but colocated is another attempt at pooling and optimizing resources in the ICU.

INTENSIVE CARE COST

Intensive care is expensive since this field demands an interdisciplinary approach along with high-technology monitoring and interventions.¹¹ The high-capital cost of equipments, salaries and wages of healthcare workers and expensive drugs and consumables, keep the cost of intensive care beyond the reach of many people. There are very few

cost studies on intensive care from India.^{23–25} The computed cost of a “critical illness” varies not only due to the type of illness and illness severity, but also on where care has been provided (public or private) and how costing was done (direct and indirect cost vs. fixed and variable cost). In one of the earliest studies on cost from India published in 1999,²³ the cost per survivor was estimated to be ₹17,029 (average cost per day of ₹1,973), treated in a multidisciplinary ICU of a tertiary care public hospital. In a more recent study in a respiratory ICU in North India, published in 2013, the cost was estimated to be ₹10,364 per day.²⁴ In a study from Christian Medical College, Vellore, published in 2015,¹⁶ the total cost of treatment for a critical illness (with a median stay of 7 days) was around ₹132,000, which included bed charges, nursing and professional fees, laboratory tests, radiology, blood products, oxygen and medication. In this study, the authors observed that the cost of treatment was significantly ($p = 0.0001$) higher during the first 3 days of ICU admission (₹19,218 per day) than in the subsequent days (₹14,690 per day).

Cost cannot be measured only in terms of money paid toward treatment but also needs to be looked at in terms of indirect medical and nonmedical costs. In one study from India, this cost was estimated to be around ₹40,000 in a semiurban setup, in addition to direct medical costs;²⁶ the low-cost estimate attributed to the large proportion of patients and families who belonged to the lower socioeconomic status. In addition to direct and indirect medical costs, the component of intangible cost of a critical illness, which is generally not assessed, transcends monetary value.

The cost of critical care must also be looked at in the context of family earnings. In one study, the total family earnings per annum in two-thirds of the patients admitted was estimated to be less than the total direct medical cost of intensive care.²⁶ This was further reflected in the family's willingness-to-pay assessments where families were willing to contribute to only 53% of the total cost of treatment, this despite the family borrowing heavily to support treatment.^{16,26} This results in a huge burden of subsidy that falls on the healthcare provider. This burden, while easier to be supported by nonprofit organizations (as money is allocated for charity or subsidy), may be difficult to support in the for-profit sector.

How can the Burden of Intensive Care Unit Cost be reduced?

Intensive care unit cost can be reduced by: (i) resource pooling, (ii) improve, adapt and overcome, (iii) cost minimization, and (iv) health insurance and schemes.

As outlined above, resource pooling of man, machine, and material (the three dimensions of cost) will help to optimize ICU resources and potentially translate to lower capital cost and manpower cost. This cost benefit can be passed on to the patient. Improve, adapt, and overcome is another strategy that can be successfully employed to indigenously develop

equipments, consumables, and drugs at lower production and marketing cost.

Cost minimization is probably another way of looking at alternative treatments or strategies that may result in cost savings.²⁷ Cautious and judicious application of therapies that have been shown to work in developed countries may not be universally applicable in the Indian context. For example, implementation of daily interruption of sedation in our setting where 1:1 nursing may not always be possible can be associated with higher self-extubation rates, need for reintubation, and prolongation of hospital stay, thereby increasing cost. Strategies of tight glycemic control, at the time when it was recommended, was resource intense and tended to reduce nurse time to other more important activities of care. In the absence of 1:1 nursing, delivery of continuous feeds through gravity assisted means or low-cost feeding pumps reduced the time taken by nursing staff to stand at the bedside to give bolus feeds with utilization of such time for other activities. Such improvisation to meet local needs is essential to keep ICU costs down and improve care so that outcomes can be optimized.

Another bane of intensive care in India is the high incidence of nosocomial infections. This is compounded by the high level of resistance of microorganisms to first second line antibiotic therapy, which in turn escalates treatment costs. In a recent study from Christian Medical College, Vellore,²⁸ it was found that infections acquired during ICU stay were associated with almost a doubling of cost (median ₹92,893 vs. 180,469) and hospital stay (12.4 vs. 21.8 days). Interestingly, such infections were not associated with increased mortality. The incidence of ICU-acquired infections in developing countries is higher than in developed countries and this adds significantly to cost. Antimicrobial stewardship, rigid enforcement of infection control practices, appropriate management of central venous lines, and measures to reduce ventilator-associated pneumonia would help to keep ICU cost down.

Health schemes initiated by the government have also played a role in mitigating cost for patients from a poorer socioeconomic background. For example, the Tamil Nadu Chief Minister's Scheme provides assistance to people from a low-socioeconomic background by health insurance through a third party. Although the quantum of assistance is limited, such support reduces the risk of patients from being pushed down the poverty line.

CONCLUSION

Meeting ICU cost in resource-limited settings is a challenging task. A multifaceted approach is required not only to reduce the cost of intensive care but also to provide adequate resources and manpower as well as focus on interventions to reduce hospital-acquired infections. The 10 major priorities for intensive care in India outlined in a recent publication is an important step forward to meet the needs of our country.²⁹ This involves organization of critical care services,

effective prehospital care, accreditation of ICUs, antibiotic resistance, disaster preparedness, making intensive care affordable, education and manpower development, knowledge translation, and end-of-life care.²⁹ However, the more important philosophical question always remains. Is intensive care cost effective in low-resource settings? A recent study from a middle income country with limited access to ICU appears to suggest so.³⁰ This study reported that provision of intensive care was associated with a median number of life years gained per patient of 30 (inpatient quality reporting 16–40) with a quality of life index of 0.64, translating to 18 quality-adjusted life years.³⁰ Although such information is not available from India, these results coupled with the enthusiasm from the critical care community in India offers hope for those who require these services in India.

REFERENCES

1. Dondorp AM, Iyer SS, Schultz MJ. Critical care in resource-restricted settings. *JAMA*. 2016;315(8):753-4.
2. Dondorp AM, Haniffa R. Critical care and severe sepsis in resource poor settings. *Trans R Soc Trop Med Hyg*. 2014;108(8):453-4.
3. Jayaram R, Ramakrishnan N. Cost of intensive care in India. *Indian J Crit Care Med*. 2008;12(2):55-61.
4. Rajagopal D, Moha R. (2015). India's disproportionately tiny health budget: A national security concern? [online] Available from: <http://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/indias-disproportionately-tiny-health-budget-a-national-security-concern/articleshow/49603121.cms>. [Accessed September, 2016].
5. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. *Lancet*. 2010;376(9749):1339-49.
6. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000, an analysis of bed numbers use and costs. *Crit Care Med*. 2004;32(6):1254-9.
7. van Zyl-Smit R, Burch V, Willcox P. The need for appropriate critical care service provision at non-tertiary hospitals in South Africa. *S Afr Med J*. 2007;97(4):268-70.
8. The World Bank. Health expenditure, total (% of GDP). [online] Available from: <http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS>. [Accessed September, 2016].
9. Sharma NC. (2016). India's health woes: Budget for the National Health Mission remains stagnated at Rs 19,000 crore. [online] Available from: <http://indiatoday.intoday.in/story/indias-health-woes-budget-for-the-national-health-mission-remains-stagnated-at-rs-19-000-crore/1/609824.html>. [Accessed September, 2016].
10. Anbalagan M, Gurusamy M. Performance evaluation of 108 ambulances in India. *IJMSR*. 2015;4(3):24-7.
11. Murthy S, Adhikari NK. Global health care of the critically ill in low-resource settings. *Ann Am Thorac Soc*. 2013;10(5):509-13.
12. Murthy S, Leligowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. *PLoS One*. 2015;10(1):e0116949.
13. Firth P, Ttendo S. Intensive care in low-income countries—a critical need. *N Engl J Med*. 2012;367(21):1974-6.
14. Baker T. Critical care in low-income countries. *Trop Med Int Health*. 2009;14(2):143-8.
15. World Health Organization. (2007). Ethical considerations in developing a public health response to pandemic influenza. [online] Available from: www.who.int/csr/resources/publications/WHO_CDS_EPR_GIP_2007_2c.pdf. [Accessed September, 2016].
16. Thomas K, Peter JV, Christina J, et al. Cost-utility in medical intensive care patients. Rationalizing ongoing care and timing of discharge from intensive care. *Ann Am Thorac Soc*. 2015;12(7):1058-65.
17. Carlon GC. Just say no. *Crit Care Med*. 1989;17(1):106-7.

18. Groeger KS, Bach PB. Consider saying yes. *Crit Care Med*. 2003;31(1):320-1.
19. Lecuyer L, Chevret S, Thiery G, et al. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. *Crit Care Med*. 2007;35(3):808-14.
20. Landon E, Howell MD. The utility of utility scores. *Ann Am Thorac Soc*. 2015;12(7):976-7.
21. Vanberkel PT, Boucherie RJ, Hans EW, et al. (2009) Efficiency evaluation for pooling resources in health care. [online] Available from: <http://doc.utwente.nl/67543/1/memo1902.pdf>. [Accessed September, 2016].
22. Vanberkel PT, Boucherie RJ, Hans EW, et al. Efficiency evaluation for pooling resources in health care. *OR Spectrum*. 2012;34:317-90.
23. Parikh CR, Karnad DR. Quality, cost, and outcome of intensive care in a public hospital in Bombay, India. *Crit Care Med*. 1999;27(9):1754-9.
24. Shweta K, Kumar S, Gupta AK, et al. Economic analysis of costs associated with a respiratory intensive care unit in a tertiary care teaching hospital in Northern India. *Indian J Crit Care Med*. 2013;17(2):76-81.
25. Kulkarni AP, Divatia JV. A prospective audit of costs of intensive care in cancer patients in India. *Indian J Crit Care Med*. 2013;17(5):292-7.
26. Peter JV, Thomas K, Jeyaseelan L, Yadav B, Sudarsan TI, Christina J, et al. Cost of intensive care in India. *Int J Technol Assess Health Care*. 2016;32(4):241-245.
27. Higgins AM, Harris AH. Health economic methods: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. *Crit Care Clin*. 2012;28(1):11-24.
28. Chacko B, Thomas K, David T, et al. Attributable cost of a nosocomial infection in the intensive care unit: A prospective cohort study. *World J Crit Care Med* 2016; In press.
29. Divatia JV, Iyer S. Ten major priorities for intensive care in India. *Intensive Care Med*. 2015;41(8):1468-71.
30. Cubro H, Somun-Kapetanovic R, Thiery G, et al. Cost effectiveness of intensive care in a low resource setting: A prospective cohort of medical critically ill patients. *World J Crit Care Med*. 2016;5(2):150-64.

Severity of Illness Scores and Their Role in Assessing Intensive Care Unit Costs

Dilip R Karnad, Sanjith Saseedharan

INTRODUCTION

In most hospitals, intensive care unit (ICU) beds form 10 to 20% of the inpatient bed strength but account for a third of the total inpatient cost.^{1,2} It is estimated that only 10% of ICU beds in India are in government-run hospitals.³ Unlike in developed countries, government spending accounts for approximately 17% of healthcare expenses, 20% of the population is covered by some form of health insurance and a vast majority of patients pay out-of-pocket for inpatient costs.^{2,3} The recently published Indian Intensive Care Case mix and Practice Patterns (INDICAPS) study revealed that 80.5% of 4,038 patients admitted to 124 Indian ICUs were self-paying.⁴ Thus, besides consequences of morbidity and mortality from critical illness, cost of ICU care can also have a major financial impact on the family of an average ICU patient. According to the National Sample Survey Office of India, the cost of medical treatment has outpaced inflation in rural and urban India.⁵ As a result, there is increasing focus on cost-effectiveness and cost-benefit analysis of healthcare. Comparisons between costs in various health care systems are often made. It is, therefore, important to understand various factors that determine ICU costs and how comparisons can, or cannot be made between various hospitals or healthcare models to decide if one model is superior to another. This article focuses on how case mix, diagnosis in individual patients, and the quality and quantity of care delivered in an ICU can influence ICU costs.

FIXED AND VARIABLE INTENSIVE CARE UNIT COSTS

Intensive care unit cost can be divided under several heads based on the purpose of the analysis. Cost may be divided into indirect cost which would include costs shared between different units in the hospital (e.g., real estate, electricity, use of lifts, water supply, administration, security) while direct cost would be cost incurred on the unit being studied; the unit could be an ICU, or on a more micro-level, an individual

patient.⁶⁻⁸ When looking at costs at individual patient level, costs can be divided in fixed costs that are incurred regardless of ICU occupancy (indirect charges plus bed costs, basic wages, cost of equipment and their depreciation value, maintenance, linen, etc.) and variable costs which would include costs varying with occupancy rates and needs of individual patients which in turn would depend on the diagnosis, organ dysfunction, need for consultation with different specialties, use of mechanical ventilation, renal replacement therapy, extracorporeal therapies, medications, blood products, nutrition, laboratory tests, radiological imaging, length of ICU stay, etc.⁶⁻⁸ This basic understanding of ICU cost analysis will help appreciate the role of individual patient scores in cost analysis and comparison.

INTENSIVE CARE UNIT SCORING SYSTEMS AND THEIR UTILITY

Scoring systems used in the ICU are mainly physiology based and have been devised to assess severity of illness. Scoring systems have been used since the early 1980s and have evolved greatly over the last 3 decades. Most severity scores [Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation score (APACHE), Simplified Acute Physiological Score (SAPS), Mortality Prediction Model (MPM), and Possum score] are based on anatomical, physiological, and therapeutic variables and the patient's diagnosis.⁹ Each variable in the score is given a weightage and the sum of these weighted scores gives the final score which correlates with the severity of illness and in-hospital mortality. Many updated versions of scores like the APACHE I, II, III, and IV; MPM I, II, and III, and SAPS I, II, and III have been published with increasingly sophisticated methods used for data collection, assigning weights, and creating outcome prediction models in order to make them more generalizable and improve accuracy of outcome prediction.^{9,10}

Though initially devised for predicting individual patient outcomes, these scores were found to perform poorly for predicting outcome at an individual patient level, but have

proven extremely useful to predict outcomes in groups of patients.⁹ Consequently, they are extensively used in benchmarking ICU performance by calculating standardized mortality ratios (actual mortality/predicted mortality), and also in clinical trials to ensure that only patients with a prespecified severity of illness are included in the trial, and also to confirm that patients randomized to two or more treatment arms are of comparable severity.^{9,10}

Another group of scores are the organ dysfunction scores that include sequential organ failure assessment (SOFA), organ dysfunction score (ODS), and logistic organ dysfunction score (LODS). These too have prognostic significance, but also serve to describe patient populations and in research studies to compare prevalence and severity of organ dysfunction in two treatment arms, or in different ICUs. These scores are often used in addition to the general severity scores described above, to analyze subgroups of patients for the purpose of benchmarking ICU performance.⁹

One severity scoring system, the therapeutic intervention severity score (TISS), though originally proposed as an outcome prediction model, differed from the other scores in that it assigned scores to all monitoring and therapeutic interventions performed in critically ill patients.¹¹ This was based on the premise that more severely ill patients would need more intensive monitoring and more therapeutic interventions.^{8,9,11} Thus, patients with a higher TISS score would be more ill and therefore have worse outcome. This approach had a major limitation—it did not permit comparisons of outcomes between ICUs or between countries because with different case—mix, requirements of therapeutic interventions could differ. Moreover, depending on the technology available in different ICUs, therapeutic interventions performed may differ. In a resource limited country, some interventions may not be available or rarely used (e.g., continuous renal replacement therapy versus slow extended dialysis, use of intra-aortic balloon pump, extracorporeal membrane oxygenation vs. conventional ventilation). Despite its limitation in predicting outcomes, TISS has been extensively used to quantify the care provided in ICUs or to specific groups of patients.^{12–15} The omega score and a variant of the TISS, the Nine Equivalents of Nursing Manpower Use Score have also been used for the same purpose.^{8,16,17} These scores have also been used to quantify nursing manpower requirement and are now grouped as activity scoring systems.^{8,9}

Both severity of illness scores and activity scores are useful to assess ICU workload or care requirements and have been used to standardize cost calculation.¹⁷ This is based on the premise that patients who are more critically ill, older patients, and those with more comorbidities would require higher resource allocation, longer ICU length of stay and thus higher costs.¹⁸ This approach has several benefits as well as limitations.^{8,10,17}

Need for Scores to make Cost Comparisons Meaningful

Bertolini et al. compared cost differences in managing patients with COPD in ICUs versus respiratory intermediate care units (RICU).¹⁹ They prospectively studied 60 ICU patients from 15 ICUs and 65 patients from 6 RICUs in Italy. They found that the cost of treating patients in ICUs (€1,507) was double of that for treating patients in the RICUs (€754).¹⁹ However, a closer look at the patient characteristics revealed significant differences in patient characteristics. ICU patients had a mean SAPS II score of 33.6 versus 25.7 for RICU patients. They also had lower GCS, multiple organ failure, new for vasoactive drugs. Compared to patient in the RICU, ICU patients also required more enteral or parenteral nutrition, laboratory tests, invasive lines, neuromuscular blocking drugs, and coagulation tests. However, use of mechanical ventilation, antibiotics, bacteriology, bronchodilators, and specialist consultations were comparable.¹⁹ Thus, after considering all these factors that would contribute to the variable cost of treating patients, the higher cost for treating the patients admitted to the ICU seems appropriate. This example highlights the need to interpret costs only after looking at case mix, severity scores, and activity scores.

Use of Severity of Illness Scores in Cost Analysis

The APACHE score correlates as the major determinant of the total ICU cost and the average daily cost indicating the use of higher resources and longer stays in the group of sick patients.^{17,18} This was elegantly described by Dahl et al. who used the APACHE system to make three groups of acuity of illness based on predicted mortality. They found that patients who had a predicted mortality around 10–50% incurred a higher ICU daily cost than those whose predicted mortality was <10%. Also those patients whose mortality prediction was beyond 50% had a 28% higher average daily ICU cost.²⁰

Several studies have shown that cost of treating non-survivors is higher than cost of treating survivors.²¹ Therefore, it is intuitive that groups of patients with higher severity scores will have higher mortality rates and therefore higher hospital costs.^{12,21} Adrie et al. studied cost of treating patients with sepsis in French ICU patients.²² They found that on multiple linear regression analysis that older age, emergency surgery, and APACHE II score were independently associated with higher cost. Angus et al. analyzed outcomes and associated cost of care of severe sepsis in the United States.¹² They found that the average cost of treating a patient with severe sepsis was \$22,100. The average cost increased from \$19,500 for those with one organ failure to \$32,800 for those with failure of four or more organs.¹² Moran et al. have found that the APACHE III score on the day of admission was an important variable that could be used to predict ICU cost in a multicenter Australian study.¹⁷

However, this relation between acuity of illness to cost is not completely linear.²¹ In fact, the relationship between severity scores and ICU cost is quite complicated. Breslow and Badawi used an electronic ICU database and found that severity score on admission correlates with length of stay (and therefore cost).¹⁰ However, the correlation was stronger for survivors than nonsurvivors. The authors suggested that sicker patients require longer time to recover and would consume more resources.¹⁰ On the other hand, nonsurvivors had a shorter length of stay. Thus, ICUs with better outcomes (where severely ill patients have better survival rates than predicted by their severity score) would have higher costs per patient than an ICU where more severely ill patients died.¹⁰ This observation emphasizes the importance of not only calculating day-1 severity score to describe the severity of illness of patients admitted to an ICU, but also the need to calculate the standardized mortality ratio (ratio of observed mortality/predicted mortality) before making cost comparisons.

Use of Activity Scores in Cost Analysis

Many activity scores have been used to estimate cost of intensive care. Activity scores have been more effective than severity scores in estimating ICU costs.^{8,23} The TISS system has been most extensively used for this purpose and was devised as a method to compare patient care quantitatively among patients in the intensive care unit and originally consisted of 76 activities which were assigned scores.¹¹ This was then simplified and the number of items were reduced from 76 to 28.¹¹ This modified TISS system has been used in many countries and found to be a useful predictor of ICU costs.¹³⁻¹⁵ In fact many studies have been able to estimate cost per TISS point which could be a more realistic indicator of the standardized cost of intensive care in a health care system (Table 1).^{13-15,24-27} However, cost per TISS point should only be interpreted by taking into consideration severity of illness and standardized mortality ratios.

TABLE 1 Cost per the Therapeutic Intervention Severity Score point reported in various studies

Authors	Year of publication	Country	Cost per TISS point
Moerer et al. ²⁴	2007	Germany	€33
Graf et al. ²³	2002	Germany	€36
Parviainen et al. ²⁵	2004	Finland	€34–37
Dickie et al. ²⁶	1998	United Kingdom	£25
Parikh et al. ¹³	1998	India	₹90
Hariharan et al. ²⁷	2007	Trinidad and Tobago	£13
Malstam et al. ¹⁴	1994	Sweden	\$54
Clermont et al. ¹⁵	1998	United States	\$268

TISS, Therapeutic Intervention Severity Score.

Dickie et al. in their study of 257 ICU patients from the United Kingdom demonstrated that TISS reliably measures the cost in the overall ICU population.²⁶ However, the relation of the TISS score to the individual patient cost was not very robust and the difference between the estimated cost and the actual cost differed by as much as $\pm 65\%$. Considering that activity scores may be a surrogate for variable costs and not for the fixed ICU costs, this observation is not surprising. Moran et al. studied daily TISS and omega scores and correlated them with actual ICU costs in 1,333 Australian ICU patients and found that omega score was more useful than TISS and that total cost could be predicted by omega score, APACHE III score on admission, and ICU length of stay.¹⁷ They concluded that a combination of severity scores and activity indices could more accurately predict individual patient's ICU cost.¹⁷

Scores and Cost Analysis in Indian Intensive Care Units

While a few studies have performed cost analysis in Indian ICUs,^{13,28-30} several factors need to be considered before applying scores to perform cost comparisons in various ICUs.

- The disparity of the health care system (rural vs. urban divide with respect to the resources and expertise available) prevents delivery of a uniform standard of care for a particular severity of illness
- Amount of care may vary for the same illness based on the size of the hospital even in large cities
- Wide variability in the availability, quality and cost of equipment used for various treatments (e.g., ventilators, bedside monitors), pharmacy cost between hospitals, level of training, and expertise of nurses may significantly alter total cost and cost per TISS point
- The nurse patient ratio ranges from 1:2 to 1:4 in Indian ICUs, and manpower costs accounts for 25–50% of variable ICU costs
- Finally, although severity and activity scores may help in adjusting for some of these differences in levels of care in Indian ICUs, cost differences should also take into account survival rates in ICUs being studied since cost are higher in ICUs where very severely ill patients are treated and with better outcomes.

CONCLUSION

Use of scores as a surrogate for ICU costs have limitations and, by themselves, have not been found to be useful to completely predict variable costs per patient. On the other hand, they could have an important role in comparing health care costs in different health care systems or ICUs by standardizing for case mix, severity of illness, quantity of care, and outcomes.

This should be done in five stages:

1. Are the patients admitted in the two ICUs comparable? Severity scores could be used to ensure that baseline severity of illness in patients in the two ICUs is similar.

2. Are the patterns of organ dysfunction similar? Organ dysfunction scores could be used to quantitate the number of organ systems affected and also the specific organs that will require support.
3. Are outcomes in both ICUs comparable? The standardized mortality ratios should be compared. Although baseline severity of illness is the same, higher costs in one ICU may be due to lower mortality, which correlates with greater length of ICU stay and higher cost.
4. Is the quantity of care provided in the two ICUs comparable? Use of activity scores will help in this comparison—total TISS per patient or day-1 TISS could be compared.
5. What is the cost per TISS point? Lower cost in one ICU could be because of lower quantity of care, so that cost per TISS point may be the same in both ICUs. Conversely, lower cost per TISS point would mean more efficient delivery of intensive care, provided that all previous indicators are comparable.

Finally, while standardizing costs for making comparisons is only one aspect of health economics of intensive care. However, it should not be seen independent of the primary, secondary, and tertiary healthcare system in the country or region. This is especially important when making comparisons across completely diverse healthcare systems as in international or regional comparisons.

REFERENCES

1. Kahn JM. Understanding economic outcomes in critical care. *Curr Opin Crit Care*. 2006;12(5):399-404.
2. Jayaraman R, Ramakrishnan N. Cost of intensive care in India. *Indian J Crit Care Med*. 2008;12(2):55-61.
3. Kapadia F, Kulkarni AP, Divatia JV. India: Where have we been? ICU resource allocation in the new millennium: Will we say "No"? 1st edition. Springer, New York; 2013. pp. 33-8.
4. Divatia JV, Amin PR, Ramakrishnan N, et al. Intensive care in India: the Indian intensive care case mix and practice patterns study. *Indian J Crit Care Med*. 2016;20(4):216-25.
5. Patel V, Parikh R, Nandraj S, Balasubramaniam P, et al. Assuring health coverage for all in India. *Lancet*. 2015;386(10011):2422-35.
6. Burchardi H, Jegers M, Goede M, Leititis JU. Benchmarking in the ICU: the measurement of costs and outcome to analyze efficiency and efficacy. *Evaluating Critical Care: Using Health Services Research to Improve Quality*. Springer-Verlag, Berlin; 2002. pp. 222-43.
7. Understanding Costs and Cost-Effectiveness in Critical Care: Report from the Second American Thoracic Society Workshop on Outcomes Research. *Am J Respir Crit Care Med*. 2002;165(4):540-50.
8. Jegers M, Edbrooke DL, Hibbert CL, et al. Definitions and methods of cost assessment: an intensivist's guide. ESICM section on health research and outcome working group on cost effectiveness. *Intensive Care Med*. 2002;28(6):680-5.
9. Vincent JL, Moreno R. Clinical review: Scoring systems in the critically ill. *Crit Care*. 2010;14(2):207.
10. Breslow MJ, Badawi O. Severity scoring in the critically ill: Part 2: Maximizing value from outcome prediction scoring systems. *Chest*. 2012;141(2):518-27.
11. Miranda DR, de Rijk A, Schaefeli W. Simplified therapeutic intervention scoring system: The TISS 28 items—results from a multicenter study. *Crit Care Med*. 1996;24(1):64-73.
12. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-10.
13. Parikh CR, Karnad DR. Quality, cost, and outcome of intensive care in a public hospital in Bombay, India. *Crit Care Med*. 1999;27(9):1754-9.
14. Malmström J, Lind L. Therapeutic intervention scoring system (TISS)—a method for measuring workload and calculating costs in the ICU. *Acta Anaesthesiol Scand*. 1992;36(8):758-63.
15. Clermont G, Angus DC, Linde-Zwirble WT, et al. Measuring resource use in the ICU with computerized therapeutic intervention scoring system-based data. *Chest*. 1998;113(2):434-42.
16. Szajder M, Leleu G, Buonamico G, Auvert B, Aegerter P, Merlière Y, et al. Estimation of direct cost and resource allocation in intensive care: correlation with Omega system. *Intensive Care Med*. 1998;24(6):582-9.
17. Moran J, Peisach A, Solomon P, et al. Cost calculation and prediction in adult intensive care: a ground-up utilization study. *Anaesth Intensive Care*. 2004;32(6):787-97.
18. Carson SS, Bach PB. The epidemiology and costs of chronic critical illness. *Crit Care Clinics*. 2002;18(3):461-76.
19. Bertolini G, Confalonieri M, Rossi C, Rossi G, Simini B, Gorini M, et al. Costs of the COPD. Differences between intensive care unit and respiratory intermediate care unit. *Respir Med*. 2005;99(7):894-900.
20. Dahl D, Wojtal GG, Breslow MJ, et al. The high cost of low-acuity ICU outliers. *J Healthc Manag*. 2012;57(6):421-33.
21. Berenson RA. Intensive Care Units (ICUs): Clinical Outcomes, Costs, and Decision-making (Health Technology Case Study 28), prepared for the Office of Technology Assessment, U.S. Congress, OTA-HCS-28, Washington DC, November 1984.
22. Adrie C, Alberti C, Chai-Couturier C, Azoulay É, et al. Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *J Critical Care*. 2005;20(1):46-58.
23. Graf J, Graf C, Janssens U. Analysis of resource use and cost-generating factors in a German medical intensive care unit employing the Therapeutic Intervention Scoring System (TISS-28). *Intensive Care Med*. 2002;28(3):324-31.
24. Moerer O, Plock E, Mgbor U, Schmid A, et al. A German national prevalence study on the cost of intensive care: an evaluation from 51 intensive care units. *Crit Care*. 2007;11(3):R69.
25. Parvainen I, Herranen A, Holm A, et al. Results and costs of intensive care in a tertiary university hospital from 1996–2000. *Acta Anaesthesiol Scand*. 2004;48(1):55-60.
26. Dickie H, Vedio A, Dundas R, et al. Leach RM. Relationship between TISS and ICU cost. *Intensive Care Med*. 1998;24(10):1009-17.
27. Hariharan S, Chen D, Merritt-Charles L. Cost evaluation in the intensive care units of Trinidad applying the cost-blocks method—an international comparison. *Anaesthesia*. 2007;62(3):244-9.
28. Kulkarni AP, Divatia JV. A prospective audit of costs in intensive care in cancer patients in India. *Indian J Crit Care Med*. 2013;17(5):292-7.
29. Kumar P, Jithesh V, Gupta SK. A comparative cost analysis of polytrauma and neurosurgery intensive care units at an apex trauma care facility in India. *Indian J Crit Care Med*. 2016;20(7):398-403.
30. Shweta K, Kumar S, Gupta AK, et al. Economic analysis of costs associated with a Respiratory Intensive Care Unit in a tertiary care teaching hospital in Northern India. *Indian J Crit Care Med*. 2013;17(2):76-81.

Stroke Units: Are They Cost Effective?

Kapil Zirpe, Rohit V Kodagali

INTRODUCTION

Stroke is a leading cause of death and disability worldwide.¹ It is also known to be the second most common killer amongst all noncommunicable diseases.² Stroke survivors often have to deal with severe disabilities for the rest of their life and are unable to return to their prestroke functionality. Moreover the cost of care for stroke is also high.^{3,4} From an Indian perspective, it becomes very important to prevent or minimize disabilities due to stroke.

In India, the incidence of stroke is estimated to be 145 patients per 100,000 population.⁵ This gives us an estimate of 1,700,000 stroke patients each year based on the 2011 census.⁶ While the Western countries have adopted the stroke unit concept, stroke units are predominantly available only in private hospitals in urban areas only. As of 2007, only 15 primitive stroke units existed in India.⁷

The objective of this review is to provide an insight into the utility and cost effectiveness of stroke units in India.

STROKE UNITS

A stroke unit is defined as "a dedicated, geographically clearly defined area or ward in a hospital, where stroke patients are admitted and cared for by a multiprofessional team (medical, nursing and therapy staff) who have specialist knowledge, training and skills in stroke care with well-defined individual tasks, regular interaction with other disciplines and stroke leadership."⁸

Stroke units are generally defined across seven fields of actions:⁸

1. Ensure vital functions
2. Provide early diagnostic investigations
3. Allow basic surveillance
4. Stroke-specific therapeutic interventions
5. Perform general therapeutic and diagnostic interventions
6. Start secondary prevention
7. Combine this with multiprofessional early mobilization and rehabilitation procedures.

Stroke patients admitted to hospital should receive organized care within designated stroke units staffed by a multidisciplinary team (medical, nursing, physiotherapy, occupational therapy, and speech therapy) with an active interest and expertise in stroke care.⁹

Infrastructure of a Stroke Unit

As per the guidelines laid down by the European Stroke Organization (ESO), it should ideally consist of two functionally different segments, which will be operated by the same stroke team.^{8,9}

- Segment A: Acute stroke monitoring ward:
 - At least four dedicated stroke beds are required, providing a 24 × 7 continuous monitoring of vitals like electrocardiography (ECG), blood pressure, oxygen saturation, and temperature
- Segment B: Postacute step-down stroke unit:
 - This segment should ideally include approximately twice the number of beds compared to segment A. However, the number of beds and length-of-stay varies locally and needs to be decided based on a regional approach, taking into consideration the stroke unit admissions per year. One monitored bed is recommended per 100 patients per year because the average stay on monitoring has been calculated to be 3 days.¹⁰

Most stroke patients should ideally be admitted to segment A for a minimum of 24 hours on a case-to-case basis. Confirmed stroke mimics may not need admission to segment A. Common features of a stroke unit are tabulated in table 1.¹¹

Ideally, formal multidisciplinary meetings should happen at least once a week for each patient that is admitted into the stroke unit.¹¹ Early assessment of discharge needs and a comprehensive discharge plan involving patient and caregiver is a necessity for stroke units.

Setting up a stroke unit has its own difficulties including lack of skilled personnel, lack of infrastructure, and high

TABLE 1 Features of stroke units

Assessment and monitoring	
Medical	Systematic clinical history and examination, routine investigations (mandatory)—serum biochemistry, hematology, electrocardiogram, CT investigations in selected patients—carotid Doppler, echocardiogram, MRI
Nursing	General care needs, vital signs, swallow assessment, fluid balance, pressure-area risks, neurological monitoring (Glasgow Coma Scale, National Neurological Institute of Health Stroke scale)
Therapy	Assessment of impairments and function
Early management of stroke	
Physiological management	Careful management of food and fluids (often intravenous saline over first 12–24 h) monitoring and treatment of infection, pyrexia, hypoxia, hyperglycemia
Early mobilization	Early measures to get patient sitting up, standing, and walking (preferably within first 24 h)
Nursing care	Careful positioning and handling, and pressure-area care management of swallowing problems. Avoidance of urinary catheters, if possible

CT, computed tomography; MRI, magnetic resonance imaging.

turnover of personnel.¹² However, hospitals need to overcome these administrative hurdles to pass on the significant benefits of stroke units to the patients.

STROKE UNITS VERSUS GENERAL CARE

In a recent Cochrane review performed in 2013 including 5,855 patients, admission in a stroke unit showed reductions in:

- Odds of death recorded at final (median 1 year) follow-up [odds ratio (OR) 0.87, 95% confidence interval (CI) 0.69–0.94; $p = 0.005$]
- Odds of death or institutionalized care (OR 0.78, 95% CI 0.68 to 0.89; $p = 0.0003$)
- Odds of death or dependency (OR 0.79, 95% CI 0.68 to 0.90; $p = 0.0007$).¹³

Table 2 gives the odds ratio estimates for stroke unit admissions versus alternate care in the prespecified subgroups.

As evident from table 2, outcomes were independent of patient age, sex, stroke severity at presentation or stroke type, and appeared to be better in stroke units based in a discrete ward as compared to alternative care. In effect, stroke unit admissions improve outcomes in all stroke etiologies and not only ischemic strokes.

Overall, stroke units have shown the following benefits compared to the alternate modalities of care in stroke patients.^{13–18}

TABLE 2 Analysis of patient characteristics on effectiveness of organized stroke unit care versus alternative service for the outcome of death or institutionalization by the end of scheduled follow-up

Subgroup	Log (odds ratio)	SE	Stroke Total	Control Total	Odds ratio IV, fixed, 95% CI	Odds ratio IV, fixed 95% CI
Age						<p>P interaction = 0.99</p>
Age upto 75 years	-0.342	0.251	249	234	0.71 (0.43, 1.16)	
Age over 75 years	-0.342	0.169	325	303	0.72 (0.51, 0.99)	
Sex						<p>P interaction = 0.24</p>
Male	-0.288	0.168	311	312	0.75 (0.54, 1.04)	
Female	-0.562	0.168	347	315	0.57 (0.41, 0.79)	
Stroke severity						<p>P interaction = 0.06</p>
Mild stroke	-0.274	0.194	504	448	0.76 (0.52, 1.11)	
Moderate stroke	-0.211	0.104	953	897	0.81 (0.66, 0.90)	
Severe stroke	-0.734	0.191	359	358	0.48 (0.33, 0.70)	
Type						<p>P interaction = 0.82</p>
Infarct	-0.462	0.128	795	728	0.63 (0.49, 0.81)	
Hemorrhage	-0.342	0.493	97	90	0.71 (0.27, 1.87)	
						0.01 0.1 1 10 100

IV, intravenous; CI, confidence interval.

- Reduced mortality
- Decreased dependency of stroke patients
- Higher chances of discharge to home
- Decreased length-of-stay
- Reduced costs.

QUALITY INDICATORS

While the benefits of stroke unit admissions over alternate care is very apparent, it is important to note that quality indicators of organized stroke care need to be adhered to. In the absence of formalized Indian guidelines, the ESO quality parameters for organized stroke care are listed below:⁸

- Percent of acute stroke patients treated with intravenous thrombolysis having a door-to-needle time <60 minutes: ideally, at least 80% of all patients need to be thrombolysed within 60 minutes
- Percent of all acute patients with stroke as the predominant pathology admitted to the hospital treated on the stroke unit (or the intensive care unit, if appropriate)
- Percent of brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI) in every suspected stroke
- Percent of ischemic stroke patients with antithrombotic therapy (antiplatelet medication) at discharge: at least 85% should be maintained
- Corresponding antithrombotic therapy (anticoagulation) at discharge in patients with atrial fibrillation: at least 85% should be maintained
- Percent of stroke unit patients screened for swallowing disorders.

COST EFFECTIVENESS OF STROKE UNIT

While there is no cost effectiveness study done in India, a published article has concluded that in low- and middle-income countries including India, the challenges notwithstanding, the potential gains from development of stroke units are substantial.¹² Table 3 elucidates the potential costs and benefits of stroke unit versus conventional wards.¹⁹ The cost of management of acute stroke is largely attributable to hospital care and the direct costs are largely attributable to nursing care and in-hospital overheads.²⁰ Table 4 gives the break-up of the proportion of direct costs due to the different aspects of stroke care in the hospital.²⁰ While this information

TABLE 3 Potential cost and benefits of stroke unit care versus conventional wards

Potential benefits	Potential costs
<ul style="list-style-type: none"> • Better survival • More patients regain independence • Fewer patients require home nursing care 	<ul style="list-style-type: none"> • Stroke unit staffing • ? Increased investigation and treatment cost • More intensive rehabilitation • Increased use of community service

TABLE 4 Proportion of direct costs for in-hospital care in stroke

Aspects of care	Proportion of direct costs (%)
Nursing	81
Hospital overheads	14
Investigation	2
Therapy	1.6
Medical care + drugs	0.5

is from the United Kingdom, the situation may be similar in an Indian scenario as well.

In studies performed in the United Kingdom, it was ascertained that a stroke episode costs the National Health Service (NHS) approximately £8,536 per episode.¹⁹ For every 100 patients treated, resources to the tune of £25,596 can be freed by utilizing stroke unit admissions as compared to conventional care.¹⁹

A study looking at the economic burden of stroke in India has concluded that costs related to stroke hospitalization is approximately 235,000.²¹ A study performed in the United Kingdom has shown that the incremental cost effectiveness ratio of stroke unit admission followed by early supported discharge (ESD) is £10,661 compared to general medical ward admission without ESD.²² This study concluded that stroke unit care admission followed by ESD is a cost effective strategy leading to a substantial gain in years of life saved.²²

Tummers et al. have showed in a meta-analysis of economic benefits of organized stroke care that care in stroke units is more expensive than conventional care, but has shown improved health outcomes.²³ Home-based rehabilitation leads to better health outcomes but is unlikely to lead to cost savings.²³

CONCLUSION

Stroke units reduce costs and length-of-stay are associated with better outcomes for patients irrespective of etiology and have been shown to be a cost effective intervention for stroke patients.

REFERENCES

1. WHO. (2009). World Health Statistics 2009. [online] Available from: http://www.who.int/gho/publications/world_health_statistics/2009/en/. [Accessed December, 2016].
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol*. 2007;6:182-87.
3. Bonita R, Beaglehole R. Stroke prevention in poor countries: time for action. *Stroke J Cereb Circ*. 2007;38:2871-2.
4. Padman JD, Srikanth V, Read SJ, et al. Poverty and stroke in India: a time to act. *Stroke J Cereb Circ*. 2007;38:3063-9.
5. Taylor F, Suresh Kumar K. Stroke in India Factsheet (Updated 2012). (2012).
6. Census of India: Provisional Population Totals : India: Census 2011. [online] Available from <http://censusindia.gov.in/2011-prov-results/indiaatglance.html>. [Accessed December, 2016].

7. Kaul S. Medicine Update. JAPL. 2008;18:519-28.
8. Ringelstein EB, et al. European Stroke Organisation recommendations to establish a stroke unit and stroke center. *Stroke J Cereb Circ.* 2013;44:828-40.
9. Langhorne P, Dennis MS. Stroke units: the next 10 years. *Lancet Lond Engl.* 2004;363:834-35.
10. Ringelstein EB, Müller-Jensen A, Nabavi DG, et al. Comprehensive stroke unit. *Nervenarzt.* 2011;82:778-84.
11. Langhorne P, Pollock A; Stroke Unit Trialists' Collaboration. What are the components of effective stroke unit care? *Age Ageing.* 2002;31:365-71.
12. Langhorne P, Villiers L de, Pandian JD. Applicability of stroke-unit care to low-income and middle-income countries. *Lancet Neurol.* 2012;11:341-8.
13. Stroke Unit Trialists' Collaboration. (2013). *Cochrane Database of Systematic Reviews* (Eds The Cochrane Collaboration). [online] Available from: <http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/>. [Accessed December, 2016].
14. Lannon R, Smyth A, Mulkerrin EC. An audit of the impact of a stroke unit in an acute teaching hospital. *Ir J Med Sci.* 2011;180:37-40.
15. Saposnik G, Kapral MK, Coutts SB, et al. Do all age groups benefit from organized inpatient stroke care? *Stroke J Cereb Circ.* 2009;40:3321-7.
16. Candelise L, Gattinoni M, Bersano A, et al. Stroke-unit care for acute stroke patients: an observational follow-up study. *Lancet Lond Engl.* 2007;369:299-305.
17. Krueger H, Koot J, Hall RE, et al. Prevalence of Individuals Experiencing the Effects of Stroke in Canada: Trends and Projections. *Stroke J Cereb Circ.* 2015;46:2226-31.
18. Krueger H, Lindsay P, Cote R, et al. Cost avoidance associated with optimal stroke care in Canada. *Stroke J Cereb Circ.* 2012;43:2198-206.
19. Langhorne P, Dennis M. *Stroke Units: An evidence based approach.* London: BMJ Books; 1998. Pp. 56-65.
20. Warlow CP, Gijn JV, Dennis MS, et al. *Stroke: A practical guide to management.* New Jersey: Wiley; 2001.
21. Marfatia S, Monz B, Suvarna V, et al. Treatment costs of stroke related to nonvalvular atrial fibrillation patients in India—A Multicenter Observational Study. *Value Health Reg.* 2014;3:205-10.
22. Saka O, Serra V, Samyshkin Y, et al. A. Cost-effectiveness of stroke unit care followed by early supported discharge. *Stroke J Cereb Circ.* 2009;40:24-9.
23. Tummers J, Schrijvers A, Visser-Meily A. Economic evidence on integrated care for stroke patients: a systematic review. *Int J Integr Care.* 2012;12:e193.

Regaining Quality of Life in Intensive Care Unit Survivors is Possible, but at What Cost?

Peter E Spronk

INTRODUCTION

Patients admitted to the intensive care unit (ICU) constitute a relatively small group, but consume a lot of resources with inherent costs. In the United States, up to 30% of total hospital costs are related to critical care services.¹ These ICU costs per day may be 4-6 times higher than the average daily cost in a non-ICU hospital environment, which will be influenced by the size of the ICU, staffing, and case-mix.² Nevertheless, these ICU-related costs are not very good as a predictor of final outcome, e.g., most patients recover after severe critical illness, but will become economically productive only after long rehabilitation trajectories.³ Indeed, the authors have shown in a long-term prospective cohort study in 749 Dutch patients that survivors regain their age-specific health-related quality of life (HRQOL), if corrected for natural decline.⁴ Others have shown in 109 survivors from acute respiratory distress syndrome that they suffer from exercise limitation, physical and psychological sequelae, and decreased physical quality of life at 5 years after ICU discharge, and consequently have an increased use of healthcare services with inherent extra costs.⁵

Nevertheless, this bears the question, whether the burden of ICU stay related to the disease and the related costs are balanced to the long-term quality of life gained after hospital discharge? And what about the costs related to consumption of other healthcare services like physiotherapists, occupational therapists, speech and language therapists, dieticians, and help at home? In other words, what is the cost-effectiveness of ICU treatment to our patients, if ethical aspects of decision making are not taken into account?

INTENSIVE CARE UNIT-RELATED COSTS

When considering ICU-related costs, there are many problems.⁶ No standardization exists how to measure and define costs, reimbursement does not match actual costs, incentives are frequently lacking to optimize cost-benefit and probably most important, actually measuring costs is

labor intensive, and very complicated. In addition, actual costs cannot be predicted based on admission diagnosis, which results in serious under-reimbursement when applying a diagnosis-related group (DRG)-based system.⁷⁻¹⁰ Most ICU physicians have no knowledge about cost of most items in their patients, although a majority indicated that they would appreciate a better understanding of cost-related issues in the ICU, if asked specific questions about the subject.¹¹ Cost as well as reimbursement in European ICUs is widely variable,¹²⁻¹⁵ although within country variability was not studied.

Several cost types should be considered. Direct costs are all costs related to goods and supplies, while indirect costs are related to the fact that the patient is in the ICU and is not able to maintain his economic capacity. Obviously, the latter factor is very difficult to quantify. Costs are explained by several cost-drivers, e.g., staffing, drugs, and equipment applied in patient care. One can imagine that if more drugs or machines are used on an ICU day then this will increase ICU-related costs for that particular patient on that particular day. These costs are, therefore, termed variable costs, while costs for staffing and maintaining the building and equipment are termed fixed costs, i.e., these costs are incurred anyway, irrespective of activity in the ICU based on availability.

Reimbursement

To match reimbursement to actual ICU-related costs, two approaches may be chosen: (i) a bottom-up system, where all activities at a patient level are assessed, quantified, and accumulated in a total patient-specific bill or (ii) a top-down system, where total costs are related to an ICU level, split up by predefined cost-drivers, e.g., the cost-block system in the United Kingdom including staff, clinical support services, and consumables as well as nonclinical support services, capital equipments (Fig. 1).^{16,17} Since fixed costs determine >60% of ICU-related costs, length of stay in the ICU is an important discriminating factor. Indeed, length of stay in the ICU, rather than specific patient data, explains 85-90% of interpatient

variation in hospital costs, which underlines the relevance of the use of this variable.¹⁸ It also illustrates that confidence in this generalized approach to heterogeneous patient groups is economically reasonable. In 2003, Rapoport et al. showed that if weighted length of stay was calculated, individual patient characteristics explained 26% of variation. The first day was even four times as expensive as a non-ICU hospital day, while from day 2 onwards, ICU days were approximately 2.5 times as expensive as a non-ICU hospital day.¹⁸ These data were corroborated by a more recent Japanese study demonstrating that fixed costs explained up to 89% of ICU-related costs.¹⁹

In order to improve the matching between costs and billing, one could argue that hospital-weighted days may be a reasonable approach as suggested by Rapoport, although the multipliers used in that study were rather arbitrary and deserve further study.¹⁸ Others have mentioned systems including severity of illness,²⁰ or moving toward a pay for performance (P4P) system using quality indicators like readmittance rate, incidence of central line-associated bloodstream infections or decubitus, or compliance with current guidelines.²¹⁻²³ Indeed, the Society for Critical Care Medicine published a P4P critical care task-force report expressing the need for an incentive-based reimbursement

system.²⁴ They defined five quality measures that could be expanded over time and should be re-evaluated. The American Thoracic Society also endorsed a P4P system, but stressed the problems related to a penalty-based system since some complications do occur, whatever, the measures that are taken to prevent that complication.²⁵

In the Netherlands, a simple, but foolproof and easy to check system was introduced in 2005 based on ICU calendar dates consumed during patient care in the ICU.²⁶ The basic background idea was that all things done with/to a patient in the ICU period should be included in the reimbursement fee to balance with actual costs. That system was able to reflect total costs on an aggregate level and as such is useful for negotiations with hospital administrators, insurance companies and other specialties in the hospital. To accomplish this, the ICU period had to be disconnected from other DRGs and was reimbursed as an "add-on product".^{15,27} The authors showed that DRGs severely underestimate ICU-related costs and a system based on DRGs would, therefore, result in serious under-reimbursement to hospitals. This confirms older data from the United States where the authors also concluded that a wide variability in length of stay did not match a low variability in daily ICU-related costs.⁷⁻¹⁰

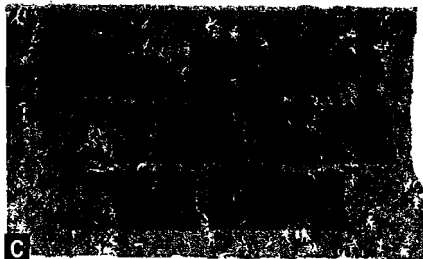
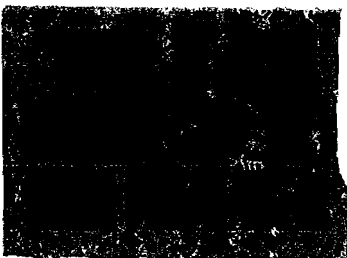
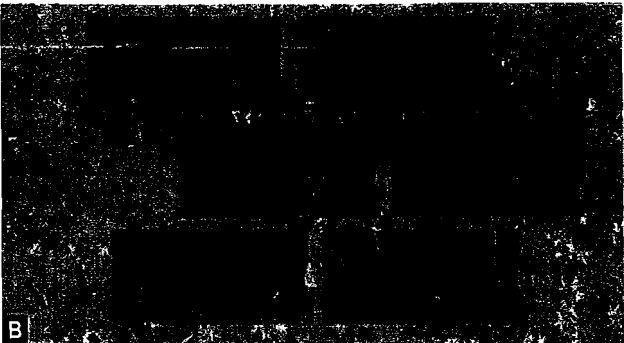
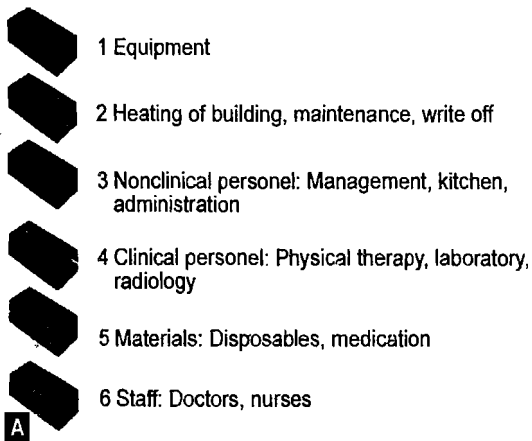


FIG. 1: Cost bricks are based on predefined cost blocks (panel A) and may differ from setting to setting (panel C). Multipliers should be used to validate the locally applied system. A, Cost blocks according to Edbrooke.^{16,17} B, Cost brick incorporating all cost blocks. C, The size and composition of cost bricks are not equal in different settings

QUALITY OF LIFE AND COSTS AFTER HOSPITAL DISCHARGE

During the recovery process of ICU survivors, the question will surface to which location or facility patients should be discharged in order to deliver services related to rehabilitation or specific care that cannot be offered in an ICU environment. Indeed, a single center study in the United States demonstrated that after 1 year follow-up of long-stay ICU survivors, patient experiences a median of four different transitions of care facilities and spent 75% of days alive in either a facility or with paid healthcare assistance. Average costs per ICU survivor for the first year accumulated to \$300,000 while total one-year accumulated costs for independent survivor was estimated at \$3.5 million.²⁸ This variability in transitions bears the question, whether it would be more proficient to centralize this posthospital care in specialized facilities. In the United States, a long-time experience exists with so-called long-term acute care (LTAC) facilities. The number of LTACs is growing exponentially, related to better ICU care and steadily decreasing mortality rates, but also to more comorbidities and increasing age of our patients. In the period from 1997 to 2006, the number of LTACs in the United States increased from 192 to 408.²⁹ The use of LTACs was driven by the fact that hospitals were paid a set amount for each patient rather than have payments determined by actual costs.³⁰ About 50% of the LTACs are currently for-profit organizations and increasingly colocated to a short-term hospital. Whether LTACs are colocated or freestanding from a hospital does, however, not seem to affect costs, although readmission rates seem lower in colocated LTACs.³⁰ This may be caused by easier inhouse consultancy by intensivists. Indeed, the care of those LTAC patients requires knowledge about multiple organ dysfunction. Single organ outclinic services and experience is frequently not sufficient to match the spectrum of problems that these chronic critically ill suffer. Also, the propensity of being readmitted to the hospital of those patients is relatively high when compared to patients those were admitted to the hospital for other reasons than acute critical illness.

The LTAC units illustrate the fact that many ICU survivors consume a lot of healthcare resources during their recovery process. A Canadian study showed that the consumption of these services proved to be strongly related to comorbidities in ARDS survivors.⁵ The investigators estimated direct medical charges and equated costs that included hospitalization, emergency room and outpatient visits, professional fees, drugs, laboratory and radiology tests and procedures, outpatient and inpatient rehabilitation, home care, and services provided in a long-term care facility. Outpatient costs declined over time from CAN\$9,000 in the first year to CAN\$4,500 in year 2, further decreasing to CAN\$700 in year 5.⁵ Similarly, the authors have shown that Dutch ICU survivors also consumed a considerable amount of healthcare services after hospital discharge.³¹ After 6

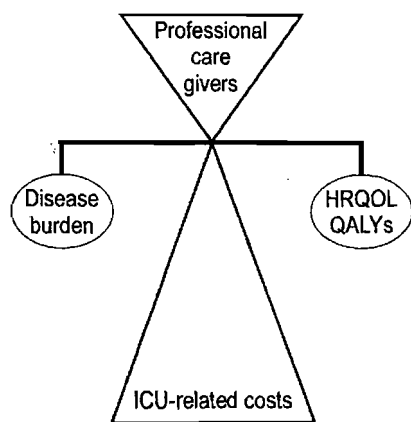
months, 50% of the patients still required daily medical nursing care at home, 42% used physiotherapy sessions, 16% required a social worker, while 16% still used the service of a professional dietician.³¹ Nevertheless, Finnish investigators concluded that despite lower HRQOL 1 year after ICU discharge, if compared to a healthy matched population, costs per 1 year predicted lifetime quality-adjusted life year (QALY) was reasonable regardless of disease severity, age, or type and duration of mechanical ventilation during ICU stay.³² This confirms earlier data from the United Kingdom and Germany where the incremental cost per QALY gained of ICU treatment was £7010 or €20,000, respectively, which was considered highly cost-effective, if compared to other commonly used health interventions.^{33,34} The reporting of the costs per QALY gained is now considered to be the standard and optimal way of reporting cost utility.⁶

INDIRECT COST EFFECTS

Patients are not able to work during critical illness and are thus economically ineffective. Moreover, <10% of patients with prolonged mechanical ventilation resume their jobs after recovery.²⁸ On the other hand, the patient being critically ill or in a devastating recovery shape drains a huge amount of efforts and energy from spouses and close family members. The financial impact of critical illness on families is often neglected and poorly understood by society. This process is inducing long-term psychological distress lasting more than a year after ICU discharge.³⁵ Indeed, serious financial problems may occur in family members of critically ill survivors, including losing a lifetime savings, and bankruptcy.³⁶ Particularly, family members of younger, poorer and more functionally dependent patients are at risk of losing most or all of the family's savings.

THINGS TO CONSIDER

From a health-economic point of view, cost benefit in any ICU patient will be highest in those patients who are admitted for a very short time independent of final outcome given the reimbursement. However, particularly in dying patients, this certainly would not balance the burden of ICU admission to the patient and family members in relation to final outcome and related costs. Should all patients be admitted to the ICU in the first place? In some cases, it would have been more humane to consider other options than intensive treatment modalities in an ICU environment, such as a palliative care in the ward. In the United States, but also in several European countries, palliative care teams are increasingly part of hospital staffing. Consultation will often lead to better understanding by patients and family members that sometimes unfortunately cure is not an attainable option and focus of caregivers should be on care instead. This will result in an optimal balance between the burden of disease, quality of life gained, and costs (Fig. 2). Indeed, daily costs spent on



HRQOL, health-related quality of life; QALY, quality-adjusted life year; ICU, intensive care unit.

FIG. 2: The balance between disease burden, attainable health-related quality of life and/or quality-adjusted life years and the influence of professional care givers on intensive care unit-related costs

ICU nonsurvivors may be even higher than daily costs spent on survivors.³⁷

Another thing to consider is the necessity for an ICU in any hospital environment, i.e., whatever acute problems may occur in patients, the ICU team will be there to take care of the problem. This service should be present irrespective of actual care being delivered to already admitted patients in any hospital. The proposed cost-brick system takes care of a simple and transparent balance between yearly costs and reimbursement. However, it lacks incentives to discharge patients from the ICU. In the United Kingdom and other countries, a shortage of ICU beds will be a strong motivator to discharge patients from the ICU, whenever possible. In contrast, this motivator is lacking in environments where the number of ICU beds is exceeding actual demand as is the case in many hospitals in the United States. This brings the question of how to include “motivators” to discharge patients from the ICU in those environments. As suggested, P4P variables may be included, but they should be carefully chosen, depending on local circumstances since they may seriously impact reimbursement and consequently the capacity to deliver a high quality of care in the ICU.

CONCLUSION

Awareness by care-givers of ICU-related costs is the first step in an effort to improve health utility in critically ill patients. Also, depending on the setting, a standardized approach is needed to make comparison between countries and settings sensible. The costbrick system that was proposed may be a first small stone in the pond. Future studies should evaluate whether a combination of a cost-brick method with P4P variables and locally validated multipliers may be a useful concept that can be used in any healthcare setting. Most importantly, such a model should incorporate costs related

to the frequently intense and long-term rehabilitation costs after hospital discharge of ICU survivors.

REFERENCES

1. Kahn JM. Understanding economic outcomes in critical care. *Curr Opin Crit Care*. 2006;12(5):399-404.
2. Jegers M, Edbrooke DL, Hibbert CL, et al. Definitions and methods of cost assessment: an intensivist's guide. ESICM section on health research and outcome working group on cost effectiveness. *Intensive Care Med*. 2002;28(6):680-5.
3. Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care: methods and human and capital inputs. *Crit Care Med*. 1996;24(7):1168-72.
4. Hofhuis JG, van Stel HF, Schrijvers AJ, et al. ICU survivors show no decline in health-related quality of life after 5 years. *Intensive Care Med*. 2015;41(3):495-504.
5. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-304.
6. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *Am J Respir Crit Care Med*. 2002;165(4):540-50.
7. Thomas F, Fox J, Clemmer TP, et al. The financial impact of medicare diagnosis-related groups. Effect upon hospitals receiving cardiac patients referred for tertiary care. *Chest*. 1987;91(3):418-23.
8. Munoz E, Josephson J, Tenenbaum N, et al. Diagnosis-related groups, costs and outcome for patients in the intensive care unit. *Heart Lung*. 1989;18(6):627-33.
9. Bekes C, Fleming S, Scott WE. Reimbursement for intensive care services under diagnosis-related groups. *Critical Care Med*. 1988;16(5):478-81.
10. Ahmad M, Fergus L, Stothard P, et al. Impact of diagnosis-related groups' prospective payment on utilization of medical intensive care. *Chest*. 1988;93(1):176-9.
11. Csomos A, Varga S, Bertolini G, et al. Intensive care reimbursement practices: results from the ICUFUND survey. *Intensive Care Med*. 2010;36(10):1759-64.
12. Gylmark M. A review of cost studies of intensive care units: problems with the cost concept. *Critical Care Med*. 1995;23(5):964-72.
13. Negri N, Sheppard L, Mills GH, et al. International Programme for Resource Use in Critical Care (IPOC)—a methodology and initial results of cost and provision in four European countries. *Acta Anaesthesiol Scand*. 2006;50(1):72-9.
14. Tan SS, Bakker J, Hoogendoorn ME, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Health*. 2012;15(1):81-6.
15. Bittner M, Donnelly M, van Zanten AR, et al. How is intensive care reimbursed? A review of eight European countries. *Ann Intensive Care*. 2013;3(1):37.
16. Jacobs P, Edbrooke D, Hibbert C, et al. Descriptive patient data as an explanation for the variation in average daily costs in intensive care. *Anaesthesia*. 2001;56(7):643-7.
17. Edbrooke DL, Ridley SA, Hibbert CL, et al. Variations in expenditure between adult general intensive care units in the UK. *Anaesthesia*. 2001;56(3):208-16.
18. Rapoport J, Teres D, Zhao Y, et al. Length of stay data as a guide to hospital economic performance for ICU patients. *Med Care*. 2003;41(3):386-97.
19. Cao P, Toyabe S, Abe T, et al. Profit and loss analysis for an intensive care unit (ICU) in Japan: a tool for strategic management. *BMC Health Serv Res*. 2006;6:1.
20. Vincent JL, Takala J, Flaatten H. Impact of reimbursement schemes on quality of care: a European perspective. *Am J Respir Crit Care Med*. 2012;185(2):119-21.
21. Jayaram R, Ramakrishnan N. Reimbursement for critical care services in India. *Indian J Crit Care Med*. 2013;17(1):1-9.
22. Nakamura I, Fukushima S, Hayakawa T, et al. The additional costs of catheter-related bloodstream infections in intensive care units. *Am J Infect Control*. 2015;43(10):1046-9.
23. de Vos ML, van der Veer SN, Graafmans WC, et al. Implementing quality indicators in intensive care units: exploring barriers to and facilitators of behaviour change. *Implement Sci*. 2010;5:52.

24. Egol A, Shander A, Kirkland L, et al. Pay for performance in critical care: an executive summary of the position paper by the Society of Critical Care Medicine. *Crit Care Med*. 2009;37(9):2625-31.
25. Kahn JM, Scales DC, Au DH, et al. An official American Thoracic Society policy statement: pay-for-performance in pulmonary, critical care, and sleep medicine. *Am J Respir Crit Care Med*. 2010;181(7):752-61.
26. van Zanten AR, van der Spoel JI, et al. IC-tarieven in kader van DBC: Een mijlpaal bereikt voor Intensive Care geneeskunde in Nederland. *Neth J Crit Care*. 2005;9(6):389-95.
27. Kwik CJ, Nierich AP, de Feiter PW, et al. Ontwikkelingen sinds de invoering van IC-tarieven in kader van DBC. *Neth J Crit Care*. 2011;15(1):38-40.
28. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med*. 2010;153(3):167-75.
29. Kahn JM, Werner RM, Carson SS, et al. Variation in long-term acute care hospital use after intensive care. *Med Care Res Rev*. 2012;69(3):339-50.
30. Kahn JM, Barnato AE, Lave JR, et al. A comparison of free-standing versus co-located long-term acute care hospitals. *PloS One*. 2015;10(10):e0139742.
31. de Jong AF, Hofhuis JG, Schrijvers AJ, et al. Demand and consumption of care in long-term ICU survivors in the Netherlands. *Neth J Crit Care*. 2010;14(4):258-61.
32. Linko R, Suojaranta-Ylinen R, Karlsson S, et al. One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. *Crit Care*. 2010;14(2):R60.
33. Ridley S, Morris S. Cost effectiveness of adult intensive care in the UK. *Anaesthesia*. 2007;62(6):547-54.
34. Graf J, Wagner J, Graf C, et al. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients—a cost-utility analysis. *Crit Care Med*. 2005;33(3):547-55.
35. Cameron JI, Chu LM, Matte A, et al. One-year outcomes in caregivers of critically ill patients. *N Engl J Med*. 2016;374(19):1831-41.
36. Covinsky KE, Goldman L, Cook EF, et al. The impact of serious illness on patients' families. SUPPORT Investigators. Study to understand prognoses and preferences for outcomes and risks of treatment. *JAMA*. 1994;272(23):1839-44.
37. Sogayar AM, Machado FR, Rea-Neto A, et al. A multicentre, prospective study to evaluate costs of septic patients in Brazilian intensive care units. *Pharmacoeconomics*. 2008;26(5):425-34.

Ethical Issues in Resource Allocation for Critical Care in Resource-limited Countries

Shivakumar S Iyer

INTRODUCTION

Ethical dilemmas pervade resource allocation in healthcare at all levels, especially in resource-limited countries. This is especially true in India and other low- to middle-income countries. In India, healthcare expenditure as a percentage of gross domestic product (GDP) has hovered around 1–1.5% for the last 5 years and is the lowest among BRIC (Brazil, Russia, India, and China) countries and higher only than Myanmar among countries of the South East Asia region.¹ It is not surprising therefore that government health expenditure in India is focused on preventive programs rather than providing in-hospital curative care including critical care.

Rationing often used synonymously with resource allocation refers to the allocation of healthcare resources in the face of limited availability and necessarily means that beneficial interventions are withheld from some individuals.² This article explores the general principles of resource allocation in healthcare at the macro level (macro-allocation) and their application to critical care units at the micro level (micro-allocation).

GENERAL PRINCIPLES

Resource allocation needs to be justified on the basis of effectiveness as compared to cost at one level and according to principles of equity and justice at another level.

Cost Effectiveness

Cost-effectiveness analysis is performed by calculating all costs and savings on the one hand and all the benefits and risks on the other. The ratio of costs/savings to benefit/risk thus obtained acts as a comparator for comparing health interventions. A cost-effectiveness analysis based on the

ethical principle of “utilitarianism” is the currently preferred method of comparing health interventions and is used both in micro- and macro-allocation of healthcare resources.

Social utilitarianism is based on three key assumptions:

1. Good is determined by consequences at the community level, which are the summation of individual utilities
2. All utilities are equal in the metric used to measure them; loss of benefit to some is balanced by the delivery of an equal benefit to others
3. Utility leads to the most efficient use of healthcare resources for the greatest community benefit.³

Costs are calculated by various methods like the United Kingdom cost blocks method, the international program for resource use (IPOC), or sometimes simply by measuring the therapeutic interventions severity score (TISS score).^{4–6} Often costs incurred by caregiver families, loss of income, and loss of property are not taken into account. These are especially important in developing countries where a single critical illness can lead to lifetime impoverishment of the family.

The effectiveness of health interventions is measured using the concepts of quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). The essence of a QALY is that it takes a year of healthy life expectancy to be worth 1, but regards a year of unhealthy life expectancy as worth less than 1. Its precise value is lower the worse the quality-of-life of the unhealthy person.⁷

Several ethical considerations are required while using QALYs to measure effectiveness of health interventions.⁸

Whose Preferences should We Use for Determining Quality-of-life?

Typically, people without disabilities tend to assign a lower quality-of-life to disabled people. This will result in fewer QALYs produced by lifesaving interventions for disabled

persons than for normal persons. On the other hand, people with disabilities will assign lesser value to interventions targeting prevention.

Lives Saved Versus Preserving Life Years as in Quality-adjusted Life Years

All things being equal, people would prefer interventions that produced equal benefits for a longer time than those that produced benefits for a shorter time. Evidence suggests that people may give more weightage even to benefits for a shorter period provided those benefits are considered significant. The controversy over life years versus lives saved, however, is far from settled.

Should the Group that Evaluates the Benefit of an Intervention be Randomly Selected or Should It Be the Group with the Particular Disability or Disease?

Persons without disabilities generally evaluate the quality-of-life with a particular disability as significantly worse than do persons who have that same disability, thus producing lesser QALYs for that intervention. This may be because of lack of understanding of the quality-of-life of individuals with disability by individuals who do not have any disability. Using individuals with disability to evaluate interventions for that disability may, however, result in lesser weightage being given to interventions not used on prevention and rehabilitation.

What Costs Should Count in Health Cost-effective Analysis?

Controversy arises whether the indirect economic costs of a health intervention should figure in calculating the costs of a health intervention direct. From a utilitarian point of view all direct and indirect costs must be accounted for. World Health Organization (WHO), however, uses the “separate spheres” view at the macro-level to separate out the health costs or benefits to individuals from the economic effects in general as otherwise people would be viewed solely as means.⁹

Should Life Years Be Age Weighted?

Alan Williams suggests that fairness that individuals should each receive a “fair innings of QALYs in their lives.”⁷ The earlier a preventable death occurs and the worse a person’s past health the greater is the unfairness the person suffers. Thus the younger a person is the greater is the moral urgency of providing him the health intervention in question. This, however, is by no means universally accepted as it may be viewed as unfair to older individuals.

Should Health Benefits/Costs Be Discounted?

The idea behind discounting costs is that the same amount of money is worth more, if received today than say in 10 years because it can be invested at the market rate of interest if received today. Health benefits, however, cannot be viewed similarly. For example, a vaccination program will save many more lives in the future at a lesser cost than say treating pneumonias at present. However, if we were to apply a discount to the lives saved in future by vaccination, then we would prefer treating pneumonias with antibiotics in the present. This approach would tend to place preventive programs like vaccination at a disadvantage as compared to curative programs using interventions like antibiotics. Discounting health benefits as opposed to costs is, therefore, considered controversial but nevertheless needs to be taken into account.

Competing Ethical Principles for Resource Allocation

While cost-effective analyses based on the principle of utilitarianism dominate discussions about resource allocation at the macro-level there are several other competing ethical principles in resource allocation both at the macro- and micro-level (Table 1).

To Each an Equal Opportunity—Egalitarianism

Egalitarianism or offering equal or fair chances to everybody either based on a lottery or on a first come first served basis seems intuitively right and has been favored by the general public in limited surveys.¹⁰ Egalitarianism offers fair chances to everyone to avail beneficial interventions but the result may not always be the best outcome for both individual patients and society at large. One needs to take into account patients’ needs and likelihood of benefiting from the intervention both in the short-term and in the long-term.¹¹ The appeal of an egalitarian solution is greater when the difference in outcomes between the programs is relatively small compared to the gain or loss to individual patients.

TABLE 1 Competing ethical principles for resource allocation

Ethical principle	Explanation
Cost effectiveness—utilitarianism	To each to maximize overall quality-adjusted life years
Egalitarianism	To each an equal opportunity
Prioritarianism	To each to favor the worst-off
The rule of rescue	To save those facing imminent death

To Each to Favor the Worst-off—Prioritarianism

Priority to the worst-off satisfies our concern for justice as can be seen in the oft-quoted statement “you can tell the justice of a society by how it treats its least well-off members”, in the well-known Difference Principle in John Rawls’s theory of justice.¹² Worst-off does not always mean those that are economically worse off (the poor), it may mean those with the worse health (the sickest). The separate spheres view suggests that worst-off should be taken to mean those with worse health for the purpose of healthcare resource allocation. Giving priority to the sickest may, however, produce worse outcomes and may face the problem of providing marginal benefits to fewer people at very great costs. Prioritarianism has also been taken to mean giving priority to the young because they have had the least chance to live through their life cycle as compared to older people. This life cycle principle has been advocated in the allocation of scarce resources like ventilators in an influenza pandemic.¹³

To Save Those Facing Imminent Death—the Rule of Rescue

Humans feel a great emotional impulse to rescue those facing imminent death no matter how small the benefit or how small the chance of rescue. This has been described as the rule of rescue. One must, however, guard against false rescue especially when death is inevitable in the short-term despite the intervention. An obvious example is the use of cardiopulmonary resuscitation (CPR) in terminally ill patients. This is even more so when the patient has explicitly requested to withhold life-sustaining interventions.

FAIR PROCESSES OF RESOURCE ALLOCATION

Given the myriad moral tensions that arise in healthcare decision-making, it is important to have a multi-principle approach rather than a single-principle approach for resource allocation both at the micro- and macro-level. It is important also to use fair processes for healthcare resource allocation. Four characteristics of such fair processes have been proposed:

1. Oversight by a legitimate institution
2. Transparent decision making
3. Reasoning according to information and ethical principles that all can accept as relevant
4. Procedures appealing and revising individual decisions.

A fifth characteristic that has been proposed is meaningful public engagement.^{14,15} Such public engagement helps to explore the values of the public stakeholders and gain valuable public support for ethical resource allocation.

IMPLICATIONS FOR RESOURCE ALLOCATION IN CRITICAL CARE IN INDIA AND THE DEVELOPING COUNTRIES

The daily cost of intensive care unit (ICU) in India may be 100 times the per capita income and can result in the rapid impoverishment of affected individuals and their families.¹⁶ This fact brings in its wake a number of painful ethical dilemmas for intensivists both during triage of critically ill patients at admission and in deciding regarding withholding-withdrawing therapy in terminally ill patients at the end-of-life in ICU (Table 2). Such dilemmas may result in ethically questionable solutions like slow code on the one hand where clinicians may unilaterally take decisions perceived to be in the best interest of patients and families and practices like “leave against medical advice” (LAMA) or “discharge against medical advice” that unfairly put the onus of decision making on the family and leave patients to die without appropriate palliative care.

Persons with disability or the elderly may unfairly have to bear the brunt of rationing decisions.

Solutions to these ethical dilemmas are not easy and will require concerted effort at all levels

At the state level, increasing healthcare budget expenditure for seriously ill patients and providing minimum facilities for rescue at primary care centers along with necessary training in managing emergencies should be seen as an urgent necessity. Expanding current government insurance schemes for selected categories of critical illness like sepsis, tropical illnesses and trauma will help avoid impoverishment of poor families. Indigenization and local manufacture of expensive equipment can substantially

TABLE 2 Ethical dilemmas

Clash of ethical principles	Example of dilemma	Questionable solution
Autonomy vs. beneficence	Patient or surrogate unable to decide. Doctors convinced about lack of benefit or harm	Slow code
Beneficence vs. autonomy	Doctors convinced about benefit to patient, relatives unable/not willing to bear cost	Discharge against medical advice
Equity, distributive justice vs. autonomy	Young patient vs. elderly frail with pneumonia-requiring ventilator	Younger person receives care
Beneficence vs. autonomy	Terminally patient in cardiac arrest receives cardiopulmonary resuscitation but surrogates expressly do not want such treatment	False rescue

reduce costs. This requires collaboration between intensive care professionals, technologists, and industry and public-private partnerships.¹⁷

At the hospital level, framing appropriate policies for triage of critically ill patients and auditing such triage decisions periodically will be necessary to improve the quality-of-care provided to seriously ill patients. Policies for early identification of futility and appropriate end-of-life measures will also help to reduce unnecessary costs.¹⁸

At the individual level, training in clinical ethics for medical students both undergraduates and postgraduates and practicing clinicians and constitution of clinical ethics committees for resolving ethical dilemmas will go a long way in improving the care of our patients.

CONCLUSION

Cost effectiveness based on social utilitarianism is the currently preferred ethical principle for healthcare allocation at the macro-level (governments). A multi-principle approach incorporating utilitarianism, equal opportunity (egalitarianism), priority to the worst-off (prioritarianism), and the rule of rescue need to be employed both at the macro- and micro-level (hospitals and individuals). Fair processes including meaningful public engagement are necessary for appropriate resource allocation. Innovative solutions are needed for ethical dilemmas arising in resource allocation for seriously ill patients in resource-restricted settings at all levels.

REFERENCES

1. Central Bureau of Health Intelligence. (2015). National Health Profile 2015. [online] Available from: <http://www.cbhidghs.nic.in/writereaddata/mainlinkFile/NHP-2015.pdf>. [Accessed December, 2016].
2. Scheunemann LP, White DB. The Ethics and Reality of Rationing in Medicine. *Chest*. 2011;140:1625-32.
3. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *Am J Respir Crit Care Med*. 2002;165:540-50.
4. Negrini D, Sheppard L, Mills GH, et al. International Programme for Resource Use in Critical Care (IPOC)--a methodology and initial results of cost and provision in four European countries. *Acta Anaesthesiologica Scandinavica*. 2006;50:72-9.
5. Parikh CR, Kamad DR. Quality, cost, and outcome of intensive care in a public hospital in Bombay, India. *Crit Care Med*. 1999;27:1754-9.
6. Jayaram R, Ramakrishnan N. Cost of intensive care in India. *Indian J Crit Care Med* 2008;12:55-61.
7. Williams A. The Value of QALYs'. *Health Soc Ser J*. 1985;3.
8. Brock DW, Wikler D. Ethical Issues in Resource Allocation, Research, and New Product Development. In: Jamison DT, Breman JG, Measham AR, et al. (Eds). *Disease Control Priorities in Developing Countries*, 2nd edition. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; Co-published by New York; Oxford University Press: 2006.
9. CMH (Commission on Macroeconomics and Health). (2001). *Macroeconomics and Health: Investing in Health for Economic Development*. [online] Available from: <http://www.who.int/macrohealth/en/>. [Accessed, December, 2016].
10. Nord E, Richardson J, Street A, et al. "Who Cares about Cost? Does Economic Analysis Impose or Reflect Social Values?" *Health Policy*. 1995;34 (2):79-94.
11. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. *Lancet*. 2009;373:423-31.
12. Rawls J. *A Theory of Justice*. Cambridge, MA; Harvard University Press: 1971.
13. White DB, Katz MH, Luce JM, et al. Who should receive life support during a public health emergency? Using ethical principles to improve allocation decisions. *Ann Intern Med*. 2009;150:132-8.
14. Daniels N. Accountability for reasonableness. *BMJ*. 2000;321:1300-1.
15. Baum NM, Jacobson PD, Goold SD. "Listen to the people": public deliberation about social distancing measures in a pandemic. *Am J Bioeth*. 2009;9:4-14.
16. Kulkarni AP, Divatia JV. A prospective audit of costs of intensive care in cancer patients in India. *Indian J Crit Care Med*. 2013;17:292-7.
17. Divatia JV, Iyer S. Ten major priorities for intensive care in India. *Intensive Care Med*. 2015;41:1468-71.
18. Myatra SN, Salins N, Iyer S, et al. End-of- life care policy: an integrated care plan for the dying: A joint position statement of the Indian society of critical care medicine (ISCCM) and the Indian association of palliative care (IAPC). *Indian J Crit Care Med*. 2014;18:615-35.